The Management of Human Pharmaceuticals in the Environment

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract:

Pharmaceuticals and their metabolites, collectively known as pharmaceutically active compounds (PhACs), have been detected in surface water, groundwater, and drinking water, in a number of countries, since the mid-1990s. Pharmaceuticals can be used in human or veterinary medicine; human pharmaceuticals in the environment are the subject of this dissertation. Human pharmaceuticals enter the environment via wastewater treatment plants, after being consumed and excreted by humans, and through improper disposal, to toilets and garbage, among other routes of entry. Some PhACs have been found to have detrimental effects on aquatic organisms at low concentrations, such as the feminization of fish after exposure to low levels of 17α-ethinylestradiol, the active ingredient in the birth control pill. Others are suspected of having effects on non-target species, but the impacts of long-term exposure to mixtures of PhACs generally remain poorly understood. Nevertheless, the precautionary principle suggests that management action to mitigate the environmental impacts of PhACs should be considered and possibly implemented.

The purpose of this dissertation is to provide an analysis of precautionary management strategies to mitigate the environment impacts of human PhACs. Four underlying objectives are set. The first is to review the extant scientific understanding of human PhACs in the environment, so that this knowledge can be applied to the analysis of management strategies. The sources, transport, fate, and occurrence of PhACs are discussed, and several classes of PhACs of particular concern are highlighted. The effects of PhACs on humans and aquatic organisms are explored, in addition to the gaps in scientific understanding of PhACs in aquatic environments. Finally, a rough ranking of priority PhACs is conducted; the PhACs of greatest concern are found to be carbamazepine, clofibric acid, ifosfamid, 17a-ethinylestradiol, oxytetracycline, ciprofloxacin, and diclofenac.

The second objective is to investigate how planning and management principles and theories can be applied to the problem of PhACs in the environment. The precautionary principle and the theory of adaptive planning are identified as essential tools in this regard. The application of the precautionary principle and adaptive planning

to pharmaceuticals in the environment are discussed, and a management framework is developed.

The third objective is to determine how human PhACs in the environment can be managed at a local scale, using a case study in the Region of Waterloo. Pharmaceuticals released from two wastewater treatment plans are found entering the local environment at concentrations similar to those in other cities internationally. Social surveys indicate that residents desire management action to prevent environmental contamination by pharmaceuticals, but at a limited cost. The surveys also indicate that many residents dispose of pharmaceuticals improperly; education to encourage proper drug disposal is therefore recommended as one of several management strategies. The other two recommended management strategies target the wastewater treatment plants. In Foxboro, where the wastewater treatment plant is functioning less than optimally, optimization without technological upgrades is suggested. In Kitchener, where the plant is functioning within ministerial guidelines, ozonation is suggested as a means of improving pharmaceutical removal without exceeding residents' willingness to pay.

The fourth and final objective is to assess how human pharmaceuticals can be managed at a broad scale, such as at the national scale. Stakeholder interviews are conducted with the purpose of gaining a deeper understanding of possible management strategies. A policy analysis is conducted to determine which combinations of management strategies are likely to optimally address the problem of PhACs in the environment, and some policy packages are recommended for implementation by governments – in particular, multiple levels of government in Canada.

This dissertation is among the first research efforts to investigate the management of pharmaceuticals in the environment. Few efforts to date have combined natural scientific research, social scientific research, and an understanding of planning and management theories, to explore policy and management options for this issue. It is hoped that this research will provide assistance to various governments grappling with pharmaceuticals in the environment. Furthermore, the research provides insight into how environmental problems surrounded by high levels of scientific uncertainty can be managed. The framework for precautionary decision making developed in this study can

provide guidance to planners, managers and policy makers faced with the problem of uncertain environmental risk.

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Dedication:

To my family: My husband, Jason MacEwen; my parents, Uta & Juergen Doerr; and my brother, Mark Doerr, for their support and encouragement. And my son, Ian MacEwen, for bringing so much joy to my life.

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Chapter 1: Introduction

1.1. Introduction

Awareness of the problem of pharmaceuticals in the environment is increasing among scientific researchers, governments, pharmaceutical companies, and the public. Since the mid-1990s, scientists have regularly detected pharmaceuticals and their metabolites, referred to collectively as PhACs (Pharmaceutically Active Compounds), in surface water (Kolpin et al., 2002; Metcalfe, Miao, Koenig, & Struger, 2003; Stumpf, Ternes, Wilken, Rodrigues, & Baumann, 1999; Ternes, 1998), groundwater (Barnes et al., 2004; Bund/Länderausschuss für Chemikaliensicherheit (BLAC), 2003; Eckel, Ross, & Isensee, 1993; Heberer et al., 2004), and occasionally in drinking water (Boyd, Reemtsma, Grimm, & Mitra, 2003; Mittelstaedt, 2003; Stan, Heberer, & Linkerhagner, 1994). These pharmaceuticals are mainly human pharmaceuticals, the subject of this thesis, although veterinary pharmaceuticals from agricultural sources have also been detected in environmental samples (Hirsch, Ternes, Haberer, & Kratz, 1999; Lissemore, Yang, Hao, & Solomon, 2005). Human pharmaceuticals are frequently found in the waters of wealthy nations where citizens consume relatively large quantities of pharmaceuticals, especially in urban areas where dilution is minimal (Heberer et al., 2004). The presence of PhACs in natural waters represents a potential concern for both the health of ecosystems (Daughton & Ternes, 1999; Ferrari, Paxeus, Lo Giudice, Pollio, & Garric, 2003; Henschel, Wenzel, Diedrich, & Fliedner, 1997) and possibly for human health (Daughton & Ternes, 1999), although many scientists believe that human health impacts are unlikely (Christensen, 1998; Schulman et al., 2002; Webb, Ternes, Gibert, & Olejniczak, 2003). While abundant studies indicate the presence of pharmaceuticals in natural waters, very little is known about the impacts of these pharmaceuticals on aquatic ecosystems. Pharmaceuticals found in rivers and streams occur at extremely low concentrations and therefore are not expected to induce acute effects such as fish kills. Rather, any impacts of pharmaceuticals on aquatic species or ecosystems are expected to be subtle, long-term, and therefore difficult to detect (Daughton & Ternes, 1999; Seiler, 2002). Possibly the clearest example to date of the effects of pharmaceuticals on aquatic organisms is the feminization of male fish in rivers in the United Kingdom, due to

exposure to low levels of oral contraceptives (17α-ethinylestradiol), among other estrogenic substances that enter streams from wastewater treatment plant outfalls (Jobling, Nolan, Tyler, Brightly, & Sumpter, 1998; Larsson et al., 1999; Purdom et al., 1994). Examples of linkages between pharmaceutical contamination and effects on aquatic organisms in the field remain limited, however, and the scientific uncertainty regarding the environmental risk posed by pharmaceuticals in natural waters remains high.

While more scientific research into the problem of pharmaceuticals in the environment is clearly needed, our awareness of the problem also demands that management action be considered to mitigate any impacts of pharmaceuticals on the environment. The precautionary principle states that when a substance poses a serious threat to the environment[1], a lack of scientific certainty concerning the impacts should not be permitted to delay management action (CEPA, 1999; Commission of the European Communities, 2000; Quijano, 2003; United Nations General Assembly, 1992). This does not suggest that pharmaceuticals be banned because of potential environmental impacts. Rather, it means that academics, scientists and members of the pharmaceutical industry should begin to develop and assess strategies to address the issue of PhACs in the environment now, instead of waiting several more decades until the degree of environmental damage[1] caused by pharmaceuticals can be measured. The theory of adaptive planning tells us that under conditions of uncertainty, flexible management strategies, which can be adjusted to newly acquired information, should be implemented (Briassoulis, 1989; Holling, 1978; Lessard, 1998). Furthermore, management strategies must meet the needs of stakeholders as much as possible (Canadian Standards Association, 1997).

The overall purpose of this thesis is to analyze management strategies to mitigate the environmental impacts of human pharmaceuticals in natural waters. Within this overarching goal are several objectives, based upon a number of research question (Fig. 1.1): *1) To review the state of science with regard to pharmaceuticals in the environment, so that existing scientific knowledge can be used in developing management strategies.*

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[1] What constitutes a 'serious threat to the environment' or 'environmental damage' is subjective and is up to stakeholders, individually and as a group.

Specific research questions underlying this objective include: What is known about the sources, transport, fate, occurrence and effects of pharmaceuticals released to the environment? How much uncertainty (see Ch. 3 for discussion of uncertainty) is there in our collective understanding? What are the gaps in scientific understanding and why do these gaps exist? Which pharmaceuticals or classes of pharmaceuticals merit the greatest concern in terms of environmental impact?

2) *To explore planning and management theories and principles that can be of use in developing an appropriate risk management framework for pharmaceuticals in the environment.* Underlying research questions include: What is risk management, what are its essential elements and which forms does it take? What does uncertainty mean for the risk management process? Which theories and principles address uncertainty within a planning and management context and how do they do so? Can a risk management framework, inclusive of these theories and/or principles, be constructed and used in exploring the management pharmaceuticals in the environment, throughout this study?

3) *To assess how human pharmaceuticals in the environment can be managed at a local scale, using a case study in the Region of Waterloo, Ontario, Canada.* Research questions include: Are pharmaceuticals being released to the environment in the Region of Waterloo, and how do local concentrations compare to those in other areas? Which pharmaceuticals are being released at particularly high concentrations? What are the sources of these pharmaceuticals, and how might these sources be targeted in risk management? Are there behaviours of residents which might contribute to the release of PhACs to the environment? Are local residents interested in seeing management action taken to reduce the release of PhACs to the environment? Finally, which management strategies might be used to mitigate the release of PhACs to the environment, locally?

4) *To assess how human pharmaceuticals in the environment might be managed at a broad – mainly national -- scale.* Underlying research questions are: What are the views of stakeholders on the issue and the management of pharmaceuticals in the environment? Which management strategies meet the needs of stakeholders? Which combinations of policies/management strategies are likely to optimally address the issue, and can some of these policy packages be recommended for implementation by governments in Canada?

Purpose: to analyze management strategies to mitigate the environmental impacts of human pharmaceuticals in natural waters

Objectives:

1) *To review the state of science with regard to pharmaceuticals in the environment, so that existing scientific knowledge can be used in developing management strategies.*

PhAC sources, fate, transport, occurrence, effects?
Uncertainty?
Gaps in understanding?
Priority PhACs?

2) *To explore how planning and management theories and principles can be of use in developing an appropriate risk management framework for pharmaceuticals in the environment.*

Elements of risk management?
Uncertainty & risk management?
Planning theories, principles?
Risk management framework for PhACs?

3) *To assess how human pharmaceuticals in the environment can be managed at a local scale, using a case study.*

Local PhAC loading?
Sources of PhACs to target?
Residents' behaviors?
Residents views on management?

4) *To assess how human pharmaceuticals in the environment might be managed at a broad – mainly national -- scale.*

Stakeholder views?
Management meeting stakeholder needs?
Optimal policy package?
Policy recommendations for government?

Figure 1.1. Research purpose, objectives, and questions.

This thesis is organized to sequentially address these objectives and research questions. Chapter 2 provides an overview of scientific knowledge regarding pharmaceuticals in the environment. Chapter 3 introduces risk management, the precautionary principle and adaptive planning; concepts which are especially relevant to the problem of pharmaceuticals in the environment. The implications of the precautionary principle and the theory of adaptive planning for the development of management strategies for pharmaceuticals in the environment are discussed. Chapter 4 is a case study examining the management of human pharmaceuticals in the mid-sized Region of Waterloo, Ontario. Samples of influent and effluent from wastewater treatment plants in the Region were analyzed to determine how well pharmaceuticals were removed by the plants, and the concentrations at which PhACs were entering local surface water. Furthermore, surveys of local residents were conducted to assess local habits of pharmaceutical use, disposal, and attitudes toward the environment. Based on the results of the wastewater analyses and the surveys, recommendations are made to enhance the management of pharmaceuticals in the environment. Chapter 5 describes a consultation of international stakeholders on pharmaceuticals in the environment. Academics, government experts and representatives of the pharmaceutical industry were asked about their views regarding pharmaceuticals in the environment, including management strategies. Finally, Chapter 6 involves an analysis of policy strategies to mitigate the environmental impacts of pharmaceuticals, with a particular focus on Canada. It is hoped that the analyses conducted in this thesis will be of use to governments in two regards: first, in providing suggestions for management of the specific issue of pharmaceuticals in the environment; second, in providing guidance as to how the precautionary principle can be applied in the management of environmental problems under conditions of uncertainty.

1.2. References

Barnes, K. K., Christenson, S. C., Kolpin, D. W., Focazio, M. J., Furlong, E. T., Zaugg, S. D., et al. (2004). Pharmaceuticals and other organic waste water contaminants within a leachate plume downgradient of a municipal landfill. *Ground Water Monitoring and Remediation, 24*(2), 119-126.

Boyd, G. R., Reemtsma, H., Grimm, D. A., & Mitra, S. (2003). Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *The Science of the Total Environment, 311*, 135-149.

Briassoulis, H. (1989). Theoretical orientations in environmental planning: an inquiry into alternative approaches. *Environmental Management, 13*(4), 381-392.

Bund/Länderausschuss für Chemikaliensicherheit (BLAC). (2003). *Arzneimittel in der Umwelt: Auswertung der Untersuchungsergebnisse*. Hamburg: 61st Umweltministerkonferenz.

Canadian Standards Association. (1997). *CAN/CSA-Q850-97: Risk management: a guideline for decision-makers*. Etobicoke, ON.

CEPA. (1999). Canadian Environmental Protection Act: The House of Commons of Canada, Bill C-32, as passed by the House of Commons, June 1, 1999.

Christensen, F. M. (1998). Pharmaceuticals in the environment -- a human risk? *Regulatory Toxicology and Pharmacology, 28*, 212-221.

Commission of the European Communities. (2000). *Communication from the Comission on the precautionary principle* (No. COM (2000)1). Brussels.

Daughton, C. G., & Ternes, T. A. (1999). Pharmaceuticals and personal care products in the environment: Agents of subtle change? *Environmental Health Perspectives, 107*, 907-938.

Eckel, W. P., Ross, B., & Isensee, R. K. (1993). Pentobarbital found in ground water. *Ground Water, 31*(5), 801-804.

Ferrari, B., Paxeus, N., Lo Giudice, R., Pollio, A., & Garric, J. (2003). Ecotoxicological impact of pharmceuticals found in treated wastewaters: study of carbamazepine, clofibric acid, and diclofenac. *Ecotoxicology and Environmental Safety, 55*, 359-370.

Heberer, T., Mechlinski, A., Fanck, B., Knappe, A., Massmann, G., Pekdeger, A., et al. (2004). Field studies on the fate and transport of pharmaceutical residues in bank filtration. *Ground Water Monitoring and Remediation, 24*(2), 70-77.

Henschel, K.-P., Wenzel, A., Diedrich, M., & Fliedner, A. (1997). Environmental hazard assessment of pharmaceuticals. *Regulatory Toxicology and Pharmacology, 25*, 220-225.

Hirsch, R., Ternes, T., Haberer, K., & Kratz, K.-L. (1999). Occurrence of antibiotics in the aquatic environment. *The Science of the Total Environment, 225*, 109-118.

Holling, C. S. (Ed.). (1978). *Adaptive environmental assessment and management*. Chichester: John Wiley & Sons.

Jobling, S., Nolan, M., Tyler, C. R., Brightly, G., & Sumpter, J. P. (1998). Widespread sexual disruption in wild fish. *Environmental Science and Technology, 32*, 2498-2506.

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, M. E., Zaugg, S. D., Barber, L. B., et al. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environmental Science and Technology, 36*, 1202-1211.

Larsson, D. G. J., Adolfsson-Erici, M., Parkkonen, J., Pettersson, M., Berg, A. H., Olsson, P.-E., et al. (1999). Ethinyloestradiol -- an undesired fish contraceptive? *Aquatic Toxicology, 45*, 91-97.

Lessard, G. (1998). An adaptive approach to planning and decision-making. *Landscape and Urban Planning, 40*, 81-87.

Lissemore, L., Yang, P., Hao, C., & Solomon, K. (2005). *Are veterinary pharmaceuticals finding their way into Ontario watersheds? An exposure assessment of pharmaceuticals in surface waters within a modle watershed in Ontario.* Paper presented at the Source water protection: 12th annual international conference on the St. Lawrence River/Great Lakes Ecosystem, Cornwall, ON.

Metcalfe, C. D., Miao, X.-S., Koenig, B., & Struger, J. (2003). Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada. *Environmental Toxicology and Chemistry, 22*(12), 2881-2889.

Mittelstaedt, M. (2003). Drug traces found in cities' water. *The Globe and Mail, February 10,* p. 1.

Purdom, C. E., Hardiman, P. A., Bye, V. J., Eno, N. C., Tyler, C. R., & Sumpter, J. R. (1994). Estrogenic effects of effluents from sewage treatment works. *Chemical Ecology, 8*, 275-285.

Quijano, R. F. (2003). Elements of the precautionary principle. In J. A. Tickner (Ed.), *Precaution, environmental science, and preventive public policy* (pp. 21-27). Washington: Island Press.

Schulman, L. J., Sargent, E. V., Naumann, B. D., Faria, E. C., Dolan, D. G., & Wargo, J. P. (2002). A human health risk assessment of pharmaceuticals in the aquatic environment. *Human and Ecological Risk Assessment, 8*(4), 657-680.

Seiler, J. (2002). Pharmacodynamic activity of drugs and ecotoxicology -- can the two be connected? *Toxicology Letters, 131*, 105-115.

Stan, H. J., Heberer, T., & Linkerhagner, M. (1994). Vorkommen von Clofibrinsaure im aquatischen System -- Fuhrt die therapeutische Anwendung zu einer Belastung von Oberflachen-, Grund- und Trinkwasser? *Vom Vasser, 79*, 57-68.

Stumpf, M., Ternes, T. A., Wilken, R.-D., Rodrigues, S. V., & Baumann, W. (1999). Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. *The Science of the Total Environment, 225*, 135-141.

Ternes, T. A. (1998). Occurrence of drugs in German sewage treatment plants and rivers. *Water Research, 32*(11), 3245-3260.

United Nations General Assembly. (1992). *Report of the United Nations conference on environment and development* (No. A/CONF.151/26 Vol. I). Rio de Janeiro.

Webb, S., Ternes, T. A., Gibert, M., & Olejniczak, K. (2003). Indirect human exposure to pharmaceuticals via drinking water. *Toxicology Letters, 142*, 157-167.

Chapter 2: Scientific Understanding of PhACs in the Environment

2.1. Introduction

Pharmaceutically active compounds (PhACs) have been detected in surface water (Kolpin et al., 2002a; Metcalfe, Miao, Koenig, & Struger, 2003; Stumpf, Ternes, Wilken, Rodrigues, & Baumann, 1999; Wiegel et al., 2004), groundwater (Barnes et al., 2004; Heberer, Schmidt-Bäumier, & Stan, 1998; Holm, Rugger, Bjerg, & Christensen, 1995; Sacher, Lange, Brauch, & Blankenhorn, 2001), and drinking water (Boyd, Reemtsma, Grimm, & Mitra, 2003; Loraine & Pettigrove, 2006; Mittelstaedt, 2003; Stan, Heberer, & Linkerhagner, 1994) in a number of countries, especially developed countries, since the mid-1990s. These products include medications for human and veterinary use, as well as their metabolites. Field and laboratory evidence suggest that some PhACs may have subtle, chronic effects on the reproduction, development, and behavior of aquatic species, among other effects (Fong, 1998; Jobling, Nolan, Tyler, Brightly, & Sumpter, 1998). Effects of PhACs in drinking water on humans, while not seen as probable (Christensen, 1998; Webb, Ternes, Gibert, & Olejniczak, 2003), cannot be ruled out. Thus PhACs are environmental contaminants whose presence in the environment can be demonstrated, but whose effects remain poorly understood. While scientific understanding of PhACs in the environment remains limited, it is important that management of the issue be based on credible scientific knowledge. With the purpose of establishing a background for later discussions of management, therefore, this chapter presents a review of the state of scientific understanding of PhACs in the environment, with a particular focus on human pharmaceuticals. Sources, transport, fate, and effects of PhACs are discussed, in addition to technologies to remove PhACs from water/wastewater.

2.2. History of PhACs in the environment

Interest in the environmental impacts of PhACs in natural waters has emerged in the past decade, particularly in developed countries, where large quantities of pharmaceuticals are consumed by humans and are used in agriculture. Concerns about environmental contamination by pharmaceuticals were first raised in the 1970s (Tabak & Brunch, 1970). In the 1980s, some preliminary analyses and estimates of pharmaceutical

concentrations in surface water and potable water were performed (Richardson & Bowron, 1985).   Only since the 1990s has technology became sufficiently advanced for researchers to quantify PhAC concentrations in aquatic samples at low µg/L and ng/L levels (Stan & Heberer, 1997; Stan et al., 1994). There has been a gradual increase in the detection of PhACs in aquatic environments. By 1996, 25 PhACs had been identified in aquatic environments, but this number increased to 68 by 1999 (Jorgensen & Halling-Sorensen, 2000) and to more than 80 by 2002 (Heberer, 2002a). While increased detection of PhACs in the environment was largely due to improvements in analytical methodology and technology for measuring low concentrations of PhACs in water, greater urban density and the increasing use of pharmaceuticals, may also have contributed to the trend (Heberer, 2002a).

2.3. Sources, transport, and fate of PhACs

PhACs enter aquatic environments via a number of routes (Figs. 2.1 & 2.2). Pathways through which PhACs reach natural waters differ depending on the use of the pharmaceutical, specifically whether the parent pharmaceutical is a human pharmaceutical or a veterinary pharmaceutical.

The most common pathway followed by human PhACs is consumption, followed by excretion to a sewage collection system (from a home, hospital, etc.), treatment at a wastewater treatment plant (WWTP) and release to surface water as wastewater effluent (Fig. 2.1). The degree to which pharmaceuticals are metabolized in the body varies; 80-90% of the antibiotic amoxicillin is released in the parent form, but only 3% of carbamazepine is excreted unchanged (Bound & Voulvoulis, 2004). Fourty-five to sixty-two percent of the drug ciprofloxacin is excreted in human urine, while another 15-25% is excreted in the feces (Golet, Xifra, Siegrist, Alder, & Giger, 2003). When pharmaceuticals are metabolized to inactive conjugates in the digestive tract through glucuronidation, they serve as reservoirs of pharmaceutically active compounds. The conjugates are frequently cleaved in wastewater treatment systems and sewers, causing the active parent pharmaceutical to be released (Baronti et al., 2000; Hirsch, Ternes, Haberer, & Kratz, 1999; Ternes, 2001). Pharmaceutical metabolites themselves have also

been detected in environmental water samples (Gross, Montgomery-Brown, Naumann, & Reinhard, 2004; Winkler, Lawrence, & Neu, 2001).

The loading of PhACs to the environment after consumption and excretion is largely dependent on the nature of the wastewater treatment plant (WWTP) where the
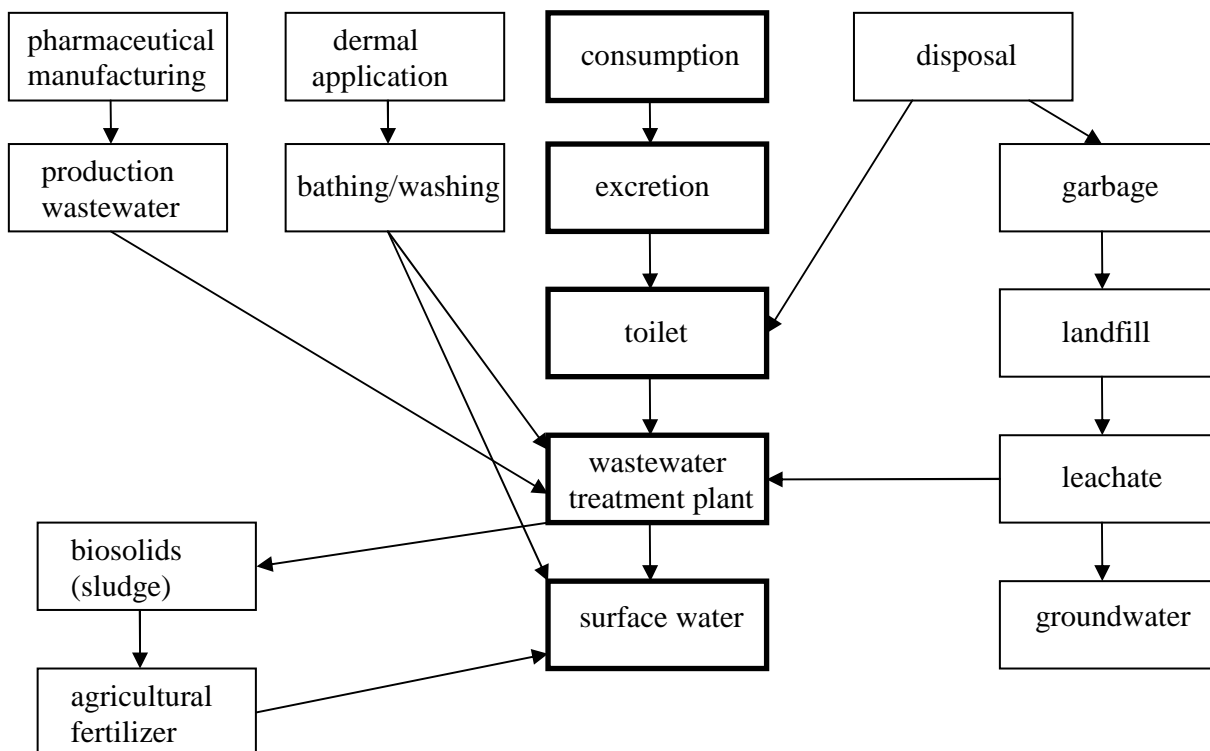
Figure 2.1. Some major routes of entry of human PhACs into the aquatic environment. The most common route of entry is via consumption.

PhAC-contaminated sewage is treated. Conventional, secondary sewage treatment involving coagulation/flocculation/sedimentation, successfully removes some PhACs, such as ibuprofen and salicylic acid (Kimura, Hara, & Watanabe, 2005; Lee, Sarafin, Peart, & Svoboda, 2004; Lindqvist, Tuhkanen, & Kronberg, 2005; Snyder, Westerhoff, Yoon, & Sedlak, 2003). Other PhACs, however, such as the anticonvulsant carbamazepine, the lipid regulator gemfibrozil, the analgesic diclofenac and the drug metabolite clofibric acid are not effectively degraded in most WWTPs (Table 2.1)

PhACs	Half-life (days)	Reference	WWTP removal (%)	Reference
Acetaminophen	3.1[1&4]	Löffler, Römbke, Meller, & Ternes, 2005	>98 8.7	Ternes, 2001 Han, Hur, & Kim, 2006
Amoxycillin			75 - 100	Castiglioni et al., 2006
Atenolol			10-55	Castiglioni et al., 2006
Bezafibrate			75 51 51 15-87	Ternes, 2001 Hua, An, Winter, & Gallert, 2003 Lindqvist et al., 2005 Castiglioni et al., 2006
Carbamazepine	No degradation[1] 100[1] 328[1&2]	Tixier, Singer, Oellers, & Müller, 2003 Andreozzi, Raffaele, & Nicklas, 2003 Löffler et al., 2005	7 8 <40 0 91	Ternes, 1998 Heberer, 2002b Heberer & Feldmann, 2005 Castiglioni et al., 2006 Han et al., 2006
Ciprofloxacin	> 21 months[3]	Golet et al., 2003	88 96 60-63	Golet et al., 2003 Lindberg et al., 2006 Castiglioni et al., 2006
Clarithromycin			0	Castiglioni et al., 2006
Clofibric acid	No degradation[1] 100[1] >4[1] 119[1&4]	Tixier et al., 2003 Andreozzi et al., 2003 Packer, Werner, Latch, McNeill, & Arnold, 2003 Löffler et al., 2005	51 0 0 30 80	Ternes, 2001 Heberer, 2002b Hua et al., 2003 Castiglioni et al., 2006 Han et al., 2006
Diazepam	311[1&4]	Löffler et al., 2005		
Diclofenac	5.0[1] 8[1] <1[1]	Andreozzi et al., 2003 Tixier et al., 2003 Packer et al., 2003	0 69 17 21 26 <15 24	Lee et al., 2004 Ternes, 2001 Heberer, 2002b Hua et al., 2003 Lindqvist et al., 2005 Heberer & Feldmann, 2005 Han et al., 2006
EE2 (17α-ethinylestradiol)	81[2] 3.0-7.7[3]	Ying, Kookana, & Dillon, 2003 Colucci & Topp, 2001	85 ~0 65 76	Baronti et al., 2000 Ternes, 2001 Esperanza, Suidan, Wang, & Sorial, 2004 Zuelke, Duennbier, Heberer, & Fritz, 2004
Enalapril			18-100	Castiglioni et al., 2006
Erythromycin			0	Castiglioni et al., 2006
Furosemide			8-54	Castiglioni et al., 2006
Gemfibrozil			5 50 69	Lee et al., 2004 Sedlak & Pinkston, 2001 Ternes, 2001
Hydrochloro-thiazide			24-44	Castiglioni et al., 2006

[1]in surface water, [2]in aerobic aquifer material, [3]in soil, [4]in sediment

Table 2.1. Half-lives and wastewater treatment plant (WWTP) removal rates for PhACs.

PhACs	Half-life (days)	Reference	WWTP removal (%)	Reference
Ketoprofen			18	Lee et al., 2004
			78	Lindqvist et al., 2005
Ibuprofen	32[1]	Tixier et al., 2003	87	Lee et al., 2004
	<6[1&4]	Löffler et al., 2005	99	Sedlak & Pinkston, 2001
			90	Ternes, 2001
			60-70	Carballa et al., 2004
			67	Hua et al., 2003
			92	Lindqvist et al., 2005
			38-93	Castiglioni et al., 2006
			78	Han et al., 2006
Ifosfamide			~0	Kümmerer, Steger-Hartmann, & Meyer, 1997
Iopromide	7.6-69.3[1]	Kalsch, 1999	0	Carballa et al., 2004
			0	Hua et al., 2003
Lincomycin			0	Castiglioni et al., 2006
Naproxen	14[1]	Tixier et al., 2003	70	Lee et al., 2004
	<1[1]	Packer et al., 2003	66	Ternes, 2001
			40-55	Carballa et al., 2004
			0	Hua et al., 2003
			80	Lindqvist et al., 2005
Norfloxacin			97	Lindberg et al., 2006
Ofloxacin	10.6[1]	Andreozzi et al., 2003	43-57	Castiglioni et al., 2006
Oxazepam	54[1&4]	Löffler et al., 2005		
Oxytetracycline	151[4]	Hektoen, Berge, Hormazabal, & Yndestad, 1995		
Propranolol	16.8[1]	Andreozzi et al., 2003	50	Sedlak & Pinkston, 2001
			95	Ternes, 2001
Ranitidine			39-84	Castiglioni et al., 2006
Salbutamol			0	Castiglioni et al., 2006
Salicylic acid			98	Lee et al., 2004
			>99	Ternes, 2001
			90	Han et al., 2006
Sulfamethoxazole	2.4[1]	Andreozzi et al., 2003	60	Carballa et al., 2004
			17-71	Castiglioni et al., 2006

[1]in surface water, [2]in aerobic aquifer material, [3]in soil, [4]in sediment

Table 2.1 cont'd. Half-lives and wastewater treatment plant (WWTP) removal rates for PhACs.

(Heberer, 2002b; Kimura et al., 2005; Lee et al., 2004; Lindqvist et al., 2005; Sedlak & Pinkston, 2001). In a study of the effects of sewage treatment on 55 pharmaceutical agents, Ternes (1998) found an average pharmaceutical removal rate of approximately

60% for a German WWTP using clarification, aeration and addition of Fe(II) chloride. Removal rates are highly variable, however, depending on the specific operating parameters of individual wastewater treatment plants (Tauxe-Wuersch, De Alencastro, Grandjean, & Tarradellas, 2005). The modification of operating parameters of conventional, sludge-activated wastewater treatment plants, particularly the solids or sludge retention time (SRT) can enhance the removal of some microbially-degraded pharmaceuticals such as bezafibrate, but attenuation of PhACs resistant to microbial degradation, such as carbamazepine, will not be enhanced by optimization of the SRT (Clara, Kreuzinger, Strenn, Gans, & Kroiss, 2005). The use of membrane bioreactors can also increase removal of microbially degradable PhACs by allowing higher SRTs within a low-volume system (Clara et al., 2005; Kimura et al., 2005). Nitrifying bacteria may help to remove some of the more polar PhACs (Eichhorn, Ferguson, Pérez, & Aga, 2005). Treatment methods relying on microbial degradation are extremely sensitive to seasonal variation, as decreasing temperature by 10° C halves the degradation rate (Clara et al., 2005). Vieno, Tukhanen and Cronberg (2005) found that removal of PhACs in Finnish WWTPs decreased by 25% on average in the winter. Performance of WWTPs in terms of plant parameters such as BOD, COD, and nitrogen removal is a good indicator of capacity to remove PhACs (Clara et al., 2005; Vieno et al., 2005)

Specialized sewage treatment techniques such as PhAC removal by activated carbon (Adams, Wang, Loftin, & Meyer, 2002), oxidation by chlorination or ozonation (Boyd et al., 2003; Ternes et al., 2003; Zwiener & Frimmel, 2000) and membrane filtration (Boyd et al., 2003; Heberer, Feldmann, Reddersen, Altmann, & Zimmerman, 2002; Sedlak & Pinkston, 2001; Yoon, Westerhoff, Snyder, & Wert, 2006) can increase PhAC removal rates to more than 95%. However the most persistent PhACs may not be completely removed by some of these processes (Arslan-Alaton & Caglayan, 2006; Huber, Canonica, Park, & Von Gunten, 2003; Snyder et al., 2003; Zwiener & Frimmel, 2000). In particular, ozonation is more effective than chlorination (Westerhoff, Yoon, Snyder, & Wert, 2005); advanced oxidation methods (ex: O_3/H_2O_2) are more effective than ozonation alone (Huber et al., 2003; Zwiener & Frimmel, 2000); and membrane filtration is most effective (Heberer et al., 2002). Oxidation processes involving chlorination or ozonation, however, generate byproducts whose risks are even less well

understood than those of the parent PhACs, (Daughton, 2001; Snyder et al., 2003; Ternes et al., 2003). The products of naproxen chlorination have been found to be detrimental to biofilms, which has negative implications for both engineered and natural systems in which biofilms play important roles (Boyd, Zhang, & Grimm, 2005). The chlorination of acetaminophen generates toxic byproducts (Bedner & MacCrehan, 2006). Clearly, specialized wastewater treatment methods, while more effective than traditional wastewater treatment, are not without problems.

Another concern with regard to wastewater treatment is the partitioning of hydrophobic PhACs to sludge. Although this can effectively remove the more lipophilic PhACs such as 17α-ethinylestradiol from the wastewater (Taro & Kikuta, 2005), it creates the potential for groundwater or surface water contamination when sludge is spread on fields as an agricultural fertilizer (Dizer et al., 2002; Heberer, 2002a). Hydrophobic PhACs can be transported to surface water associated with organic particulate matter in runoff (Boxall, Blackwell, Cavallo, Kay, & Tolls, 2002). Furthermore repeated spreading of sludge may lead to the accumulation of PhACs in soil (Golet et al., 2003).

Other less studied, wastewater related sources of PhACs include septic systems and leaky sewage pipes. Wolf, Held, Eiswirth, and Hötzl (2004) found water containing iodinated contrast media below leaky sewage pipes in Germany. Septic systems are suspected of releasing PhACs which may contaminate groundwater; research on groundwater contamination by PhACs from septic systems is currently ongoing (pers. comm., Dr. Carol Ptacek, 2006).

Pharmaceuticals can also enter the soil and potentially contaminate groundwater, when reclaimed wastewater is used for irrigation. As water resources are depleted, particularly in arid parts of the U.S., reclaimed wastewater is increasingly becoming an important source of irrigation water and may eventually be used to generate drinking water (Daughton, 2004a, 2004b; Kinney, Furlong, Werner, & Cahill, 2006; Loraine & Pettigrove, 2006; Toze, 2006). In a study by Kinney et al. (2006), pharmaceuticals were found in soil irrigated by reclaimed wastewater. Some PhACs, such as carbamazepine and erythromycin, persisted in the soil for over 6 months. The authors suggest that such

PhACs may accumulate in soils that receive year-round irrigation from reclaimed wastewater, and may eventually migrate to the water table.

Improper disposal of unused pharmaceuticals contributes to the loading of PhACs to the environment (Fig. 2.1). Estimates of the fraction of drugs which are disposed of rather than consumed range as high as 1/3 (Greiner & Rönnefahrt, 2003). Improper disposal usually means flushing pharmaceuticals down the toilet, whereby they enter the sewage stream, or disposing drugs in the garbage, whereby they are stored in landfills. Contamination of groundwater by PhACs from landfill leachate has been documented by several researchers (Barnes et al., 2004; Eckel, Ross, & Isensee, 1993; Holm et al., 1995). Furthermore, when leachate is collected, it is often subsequently sent to a wastewater treatment plant (pers. comm.., D. Andrews, wastewater operations manager, Region of Waterloo, 2005).

Industrial spills of PhACs were once common, as the practice of dumping industrial residues was accepted. Such spills resulted in some of the major cleanup efforts sponsored by Superfund in the U.S. (Heberer, 2002a), and groundwater in some areas is still contaminated as a result of past spills (Heberer et al., 2004; Reddersen, Heberer, & Dünnbier, 2002). More recent regulations governing the disposal of industrial waste in developed countries are much stronger than several decades ago, and spills are becoming rare. Some PhACs are still released to the environment through manufacturing wastewater, including in water used to wash pharmaceutical manufacturing equipment (Balcýoðlu & Ötker, 2003; Guardabassi, Petersen, Olsen, & Dalsgaard, 1998) (Fig. 2.1). However pharmaceutical companies are devoting much effort to the development of advanced treatment plants to mitigate the entry of PhACs into wastewater from pharmaceutical manufacturing plants (AstraZeneca, 2003).

Dermally applied human pharmaceuticals can be washed into water by bathing, showering, swimming, and similar activities (Daughton & Ternes, 1999). In the case of bathing in natural waters such as lakes, pharmaceuticals can directly enter the environment (Fig. 2.1). Bathing and showering indoors causes pharmaceuticals washed from the body to enter the sewage collection system (Fig. 2.1).

Veterinary pharmaceuticals are used for agriculture, aquaculture, and for pets. Pets excrete PhACs directly onto land and the PhACs may potentially infiltrate into

aquifers or be carried to surface waters as runoff (Daughton, 2001) (Fig. 2.2). PhACs for aquaculture – mainly antimicrobials – are applied directly to the water. Consequently, 75-80% of medication for fish is released directly to the environment, without ever being consumed (Hektoen et al., 1995). PhACs used in agriculture can be excreted directly onto fields by farm animals, or manure containing PhACs may be applied to land. As a result, some PhACs are bound to the soil (Schiffer, Daxenberger, Meyer, & Meyer, 2001) where they may also be degraded by microbes in the soil and/or manure (Carlson & Mabury, 2006). Hydrophilic PhACs will easily be dissolved by rainwater and may infiltrate into underlying aquifers or may be carried to surface water as runoff. However PhACs may degrade as they migrate through the soil and the unsaturated zone, and may never reach the water table (Boxall et al., 2002). As with sewage sludge, hydrophobic PhACs from manure may be transported to surface or groundwater together with dissolved organic carbon (Boxall et al., 2002; Schiffer et al., 2001).
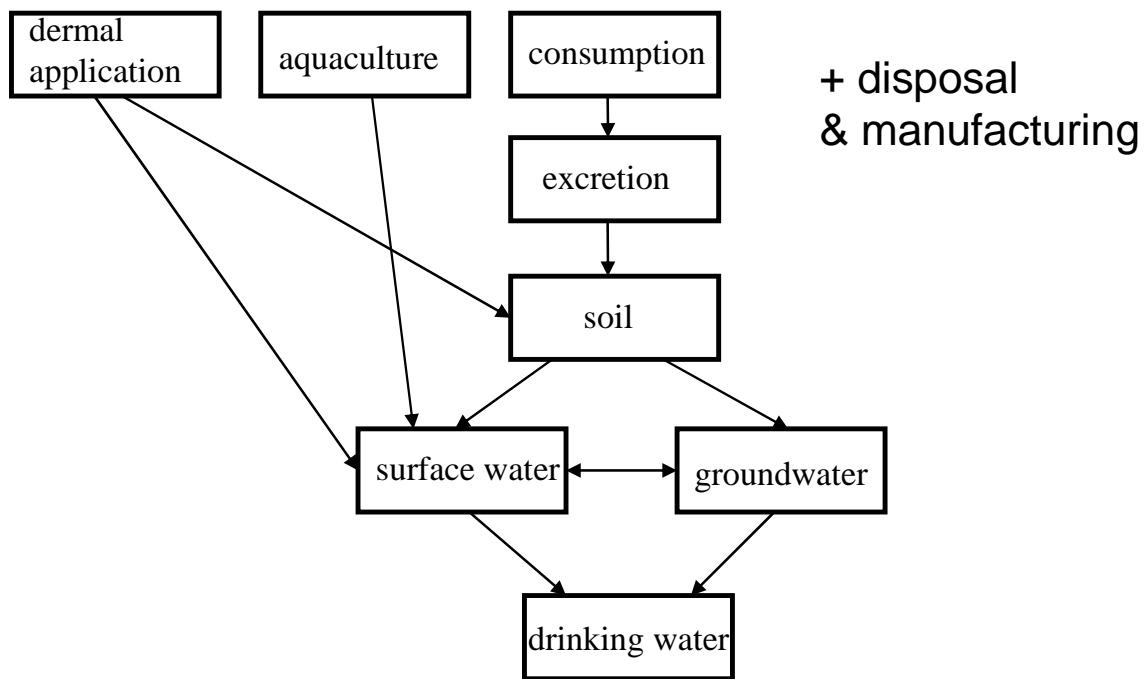
Figure 2.2. Some major routes of entry of veterinary pharmaceuticals into the environment.

Once PhACs have reached natural waters, they may degrade by a variety of mechanisms, depending on the compound. Table 2.1 provides half-lives for some pharmaceuticals in aquatic environments. Many pharmaceuticals, including the drug diclofenac, undergo photodegradation (Boreen, Arnold, & McNeill, 2003; Buser, Poiger, & Müller, 1999; Buser, Polger, & Müller, 1998; Packer et al., 2003). Humic matter can increase or decrease the rate of photodegradation of some PhACs, depending on its concentration, and nitrate can also act as a photosensitizer for some drugs (Andreozzi et al., 2004; Doll & Frimmel, 2003). Biodegradation is an important removal mechanism for the drug ibuprofen in surface water (Löffler et al., 2005; Winkler et al., 2001). Both biodegradation and photodegradation are highly sensitive to varying climatic conditions; Vieno et al. (2005) found that concentrations of pharmaceuticals in surface water were much higher in winter than in summer, due in large to the inhibition of biodegradation by cold temperatures, and photodegradation by the presence of ice and snow on the river, and limited daylight. Sorption to sediment is an important mechanism for the attenuation of hydrophobic PhACs such 17α-ethinylestradiol and diazepam in surface water/sediment (Löffler et al., 2005; Ying et al., 2003; Ying, Kookana, & Dillon, 2004), but is not a significant attenuation mechanism for some of the more polar PhACs such as diclofenac (T. Scheytt, Mersmann, Lindstädt, & Heberer, 2005), although ion exchange play a role in the attenuation of charged compounds (Lorphensri et al., 2006). Finally, some pharmaceuticals are extremely persistent and are not easily attenuated at all, such as the anti-epileptic drug carbamazepine and clofibric acid, the metabolite of the cholesterol medication clofibrate (Löffler et al., 2005; T. Scheytt, Mersmann, Leidig, Pekdeger, & Heberer, 2004; T. J. Scheytt, Mersmann, & Heberer, 2006; Tixier et al., 2003).

2.4. Classes of PhACs of concern

Several classes of PhACs are of special concern with respect to environmental impacts. Some are produced and consumed in large quantities; others are highly potent at low concentrations; and still others are extremely persistent in the environment.

2.4.1. Antimicrobials

Antimicrobials can disrupt wastewater treatment processes and have a high potential for ecosystem impacts because they are designed specifically to be toxic to bacteria (Jorgensen & Halling-Sorensen, 2000; Kümmerer, 2001). They can be hydrophobic or hydrophilic, and some bioaccumulate (Wollenberger, Halling-Sorensen, & Kusk, 2000). For instance, erythromycin has been found to have a bioaccumulation factor of 45.31 (Jones, Voulvoulis, & Lester, 2002). Erythromycin also appears to accumulate in soils (Löffler et al., 2005). It is possible that low concentrations of antimicrobials in natural waters may exert selective pressure leading to the development of antibiotic resistance in bacteria (Witte, 2000). Evidence of the transference of resistance between bacteria in wastewater and the bacteria in sludge in sewage treatment plants has been recorded (Witte, 2000). Sources of antimicrobials of special concern include a) agriculture: agriculture accounts for 50% of antibiotic use in Europe, and manure used as fertilizer represents a potential source of antibiotic contamination of surface water and groundwater (Kümmerer, 2001); b) hospitals: hospital effluent may contain sufficient quantities of antimicrobials to induce microbial resistance. Concentrations of antibiotics in the range of the MIC_{50} values of most pathogens have been found in hospital effluent, indicating the possible exertion of selective pressures on pathogenic bacteria (Al-Ahmad, Daschner, & Kümmerer, 1999; Kümmerer & Henninger, 2003). In particular, ciprofloxacin, a fluoroquinolone antimicrobial, is known to be highly toxic to bacteria (Hartmann, Alder, Koller, & Widmer, 1998), and is therefore of special concern with regard to ecosystem impacts (Bund/Länderausschuss für Chemikaliensicherheit (BLAC), 2003).

2.4.2 Synthetic hormones

Synthetic hormones have the potential to affect the endocrine systems of humans and wildlife at low levels. The main synthetic hormone found in environmental samples is 17α-ethinylestradiol (EE2), used in oral contraceptives for humans. Other synthetic hormones exist, such as mestranol, which is also used as a human oral contraceptive but has only occasionally been found in environmental samples (Heberer, 2002b). EE2 is excreted by humans as an inactive glucuronide but it is de-conjugated to the active parent in sewers and WWTPs by E.Coli (Baronti et al., 2000). Secondary wastewater treatment

removes EE2 somewhat successfully but not completely; removal rates vary between 75-85% for secondary wastewater treatment (Baronti et al., 2000; 1999; Ying, Kookana, & Ru, 2002). EE2 is primarily removed from sewage by passive sorption to sludge rather than by biodegradation, due to its log K_{ow} of 3.9-4.1 (Johnson & Sumpter, 2001). Because EE2 partitions to sludge, it may be contained in biosolids spread on fields as agricultural fertilizer, potentially entering surface water in the form of runoff or entering groundwater by leaching. Some studies indicate that EE2 in biosolids spread on agricultural fields may be degraded or diluted to concentrations below detection within days, and may therefore not reach the water table (Colucci & Topp, 2001; Lorenzen, Burnison, Servos, & Topp, 2003). A study of aquifer storage recovery by Ying, Kookana & Dillon (2004), however, determined that EE2 did not degrade significantly in aquifer material over a period of 70 days.

EE2 is a concern because it is extremely potent at very low concentrations. A concentration of 0.1 ng/L EE2 in surface water is sufficient to induce production of the female egg protein vitellogenin in male rainbow trout (Purdom et al., 1994).   In the U.K., concentrations of EE2 of up to 10 ng/L are commonly found in wastewater treatment plant effluents (Purdom et al., 1994). EE2 is suspected of being the cause of intersex fish in U.K. rivers and streams. The synthetic hormone has been found to bioaccumulate, reaching concentrations in the bile of trout exposed to sewage effluent of 10^4-10^6 times the concentrations in the surrounding water (Larsson et al., 1999).

2.4.3. Lipid regulators

Lipid regulators are among the most ubiquitous PhACs in aquatic environments. Clofibric acid, a metabolite of the lipid regulator clofibrate, was the first PhAC to be detected in tap water, at concentrations of 10-165 ng/L in Berlin (Stan et al., 1994). Clofibric acid is extremely persistent. It has a reported half-life of up to 21 years and continues to be found in environmental samples, including drinking water, even in locations where it has been removed from the market (Zuccato, Calamari, Natangelo, & Fanelli, 2000). The metabolite is incompletely removed by standard ozonation procedure for drinking water and advanced oxidation processes are required to eliminate it from

water supplies (Zwiener & Frimmel, 2000). Clofibric acid is suspected of being harmful to aquatic organisms (Henschel, Wenzel, Diedrich, & Fliedner, 1997).

Gemfibrozil has been found in drinking water in Canada (Mittelstaedt, 2003) and bezafibrate and fenofibrate have been found in German drinking water (Ternes, 2001) at ng/L concentrations. Gemfibrozil is not effectively removed by WWTPs; Lee et al. (2004) found a removal rate of 5% for Gemfibrozil in Canadian WWTPs. Although the effects of lipid regulators such as clofibric acid, gemfibrozil, fenofibrate and bezafibrate on humans at low concentrations are unknown, their occurrence in drinking water is a concern, as is their ubiquity in surface waters. Environmental levels of gemfibrozil have been found to reduce the production of sex hormones in male goldfish (Trudeau et al., 2004).

Other types of lipid regulators that have been detected in aquatic environments include the statin class of lipid regulators. Statin lipid regulators are recommended more frequently in Canada than any other lipid regulators; atorvastatin accounted for 52% of recommendations for lipid regulators in 2003 (IMS Health Canada, 2004). Atorvastatin has been detected in the effluents of several Canadian WWTPs as well as in nearby surface water (Metcalfe, Miao et al., 2003).

2.4.4. Anti-inflammatories and analgesics

Anti-inflammatories and analgesics include some of the most widely used pharmaceuticals such as the over-the-counter pain killers acetaminophen, ibuprofen and acetylsalicylic acid (ASA). They are ubiquitous in surface waters and are occasionally detected in groundwater. Anti-inflammatories and analgesics have also been found in drinking water; Ternes (2001) detected 6 ng/L diclofenac, 3 ng/L ibuprofen, and 50 ng/L phenazone in German tap water, and Vieno et al. (2005) measured 8.5 ng/L ibuprofen and 8 ng/L ketoprofen in Finnish drinking water. Anti-inflammatories of special concern include ibuprofen, which is used in large quantities and is poorly removed from raw water by ozonation (Heberer, 2002a; Zwiener & Frimmel, 2000), and diclofenac, which is ubiquitous and is relatively poorly removed by secondary sewage treatment (Table 2.1) (Lee et al., 2004; Ternes, 2001). Diclofenac has received increased attention recently as it has been found to be responsible for the death of more than 95% of the oriental white-

backed vulture population. The drug, present in dead livestock, caused renal failure in the vultures (Oaks et al., 2004). Although it is photodegradable (Buser et al., 1998), diclofenac has been found in groundwater samples (Heberer et al., 1998).

2.4.5. Antiepileptics

The anti-convulsant drug carbamazepine is frequently found in environmental samples. It has been detected in surface water at up to 1.1 µg/L (Ternes, 1998) and in groundwater at 900 ng/L (Sacher et al., 2001), and has been found in Canadian drinking water (Mittelstaedt, 2003) as well as at 30 ng/L in German drinking water (Ternes, 2001). The removal rate of carbamazepine from wastewater by a secondary sewage treatment plants has been found to be quite low, between 7-40% (Table 2.1), and its half-life has been found to be between 47-328 days (Andreozzi et al., 2003; Löffler et al., 2005). The anti-epileptics carbamazepine and primidone were found to persist and were readily transported to groundwater during bank filtration experiments (Drewes, Heberer, Rauch, & Reddersen, 2003; Heberer et al., 2004); column experiments have found virtually no retardation for carbamazepine migrating through sand (T. Scheytt et al., 2004). Carbamazepine was found to persist in soil more than 6 months after irrigation by reclaimed wastewater in Colorado (Kinney et al., 2006). Carmabazepine is so persistent that some researchers have suggested it be used as a tracer to indicate water contamination by sewage effluent (Clara, Strenn, & Kreuzinger, 2004). Ferrari et al. (2003) found a risk quotient of greater than one for carbamazepine in surface water, indicating that it could be harmful to aquatic organisms, particularly invertebrates.

2.4.6. Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine are usually prescribed as anti-depressants. They can exert a wide range of effects on aquatic organisms, especially on invertebrates (Brooks et al., 2003; Fong, 2001), inducing reactions such as the spawning of mussels (Fong, 1998). Fluoxetine has been detected at up to 0.099 µg/L in Canadian WWTP effluents, and at lower levels in Canadian surface water (Metcalfe, Miao et al., 2003).

2.4.7. Other PhACs

Beta blockers are ubiquitous and are not always removed by WWTPs. For instance, one study found that less than 50% of propranolol was removed by secondary sewage treatment (Sedlak & Pinkston, 2001). The beta blockers metoprolol was the PhAC with the highest concentrations in the Weschnitz river in a German study (2001), at > 1 µg/L. Cytostatics and immunosuppressants have been detected in WWTPs effluent but not in natural waters (Ternes, 1998). They are of concern due to their teratogenicity, mutagenicity, carcinogenicity, and genotoxicity (Sanderson, Johnson, Wilson, Brain, & Solomon, 2003). Iodinated contrast media, often used to perform X-ray exams in hospitals, spread widely in the environment and have been detected in groundwater (Putschew, Wischnack, & Jekel, 2000; Sacher et al., 2001); however they are not believed to be harmful to humans or aquatic organisms (Kümmerer, 2001; Steger-Hartmann, Länge, & Schweinfurth, 1999).

2.5. Occurrence of PhACs in surface water, groundwater, and drinking water (Table 2.2)

PhACs have been found in surface water, groundwater, and, occasionally, drinking water, in more than 10 countries, predominantly in Europe and North America (Heberer, 2002a). PhACs are ubiquitous in surface water; a study by Ternes (2001) found PhACs in 31 of 40 streams and rivers sampled. They occur more rarely in groundwater and drinking water. The same study by Ternes (2001) found 15% of groundwater samples to be contaminated by PhACs at concentrations of more than 0.1 µg/L. A number of these contaminated samples, however, were from groundwater wells under the influence of surface water (Ternes, 2001).

Class	PhAC	Conc. (μg/L)		Source	Reference
		Med.	Max.		
Antimicro-bials	Sulfametho-xazole	0.15	1.9	Surface water, U.S.	Kolpin et al., 2002a
		0.03	0.48	Surface water, Germany	Hirsch et al., 1999
		n/a	0.410	Groundwater, Germany	Sacher et al., 2001
		n.d.	0.47	Groundwater, Germany	Hirsch et al., 1999
	Anhydroery-thromycin	n/a	0.049	Groundwater, Germany	Sacher et al., 2001
	Chlortetra-cycline	0.42[*]	0.69	Surface water, U.S.	Kolpin et al., 2002a
	Roxithro-mycin	n.d.	0.56	Surface water, Germany	Hirsch et al., 1999
	Sulfanilic acid	n/a	6.47 mg/L	Landfill leachate (groundwater), Denmark	Holm et al., 1995
	Sulfachloro-pyridazine	n/a	590	Agricultural drainflow, U.K.	Boxall et al., 2002
Lipid Regulators	Gemfibrozil	0.18	0.54	WWTP effluent, Canada	Lee et al., 2004
		0.048	0.79	Surface water, U.S.	Kolpin et al., 2002a
		0.052	0.51	Surface water, Germany	Ternes, 1998
		0.066	0.112	Surface water, Canada	Metcalfe, Miao et al., 2003
		n/a	0.340	Groundwater, Germany	Heberer et al., 1998
		n/a	<0.70	Drinking water, Canada	Mittelstaedt, 2003
	Clofibric acid	n/a	0.060	Surface water, Germany	Heberer et al., 2004
		n/a	0.103	Surface water, Canada	Boyd et al., 2003
		0.066	0.55	Surface water, Germany	Ternes, 1998
		0.059	0.175	Surface water, Canada	Metcalfe, Miao et al., 2003
		n/a	7.300	Groundwater, Germany	Heberer et al., 1998
		n/a	0.125	Groundwater (raw drinking water), Germany	Heberer et al., 2004
		0.010-0.165	0.165	Drinking water, Germany	Stan et al., 1994
		n/a	0.0053	Drinking water, Italy	Zuccato et al., 2000
	Bezafibrate	n/a	0.060	Surface water, Germany	Heberer et al., 2004
		0.35	3.1	Surface water, Germany	Ternes, 1998
		0.052	0.200	Surface water, Canada	Metcalfe, Miao et al., 2003
		<LOQ	0.027	Drinking water, Germany	Ternes, 2001
	Atorvastatin	n/a	0.015	Surface water, Canada	Metcalfe, Miao et al., 2003
Anti-inflamma-tories/ Analgesics	Ibuprofen	0.48	0.97	STP effluent, Canada	Lee et al., 2004
		0.07	0.53	Surface water, Germany	Ternes, 1998
		0.141	0.790	Surface water, Canada	Metcalfe, Miao et al., 2003
		n/a	0.200	Groundwater, Germany	Heberer et al., 1998
		0.l2[**]	n/a	Drinking Water, U.S.	Loraine & Pettigrove, 2006
		n/a	0.0007	Seawater, Norway	Weigel et al., 2004
		n/a	0.0085	Drinking Water, Finland	Vieno et al., 2005
	Diclofenac	n/a	0.370	Surface water, Switzerland	Buser et al., 1998

*These median values do not include nondetects – see Till (2003)
** Mean

*Table 2.2. Occurrence of PhACs in aquatic environments: some findings of note
(n/a=not available, n.d. =below detection, LOQ=limit of quantitation,
WWTP=wastewater treatment plant)*

Class	PhAC	Conc.(μg/L)		Source	Reference
		Med.	Max.		
Anti-inflamma-tories/ Analgesics	Diclofenac	n/a	0.025	Surface water, Germany	Heberer et al., 2004
		0.15	1.20	Surface water, Germany	Ternes, 1998
		0.026	0.042	Surface water, Canada	Metcalfe, Miao et al., 2003
		n/a	0.380	Groundwater, Germany	Heberer et al., 1998
		n/a	0.590	Groundwater, Germany	Sacher et al., 2001
		n/a	0.010	Groundwater (raw drinking water), Germany	Heberer et al., 2004
		<LOQ	0.006	Drinking water, Germany	Ternes, 2001
	Propy-phenazone	0.024	0.95	Surface water, Germany	Ternes, 1998
		n/a	1.465	Groundwater, Germany	Heberer et al., 1998
	Phenazone	n/a	1.250	Groundwater, Germany	Heberer et al., 1998
		n/a	0.025	Groundwater, Germany	Sacher et al., 2001
		<LOQ	0.050	Drinking water, Germany	Ternes, 2001
	Naproxen	0.070	0.39	Surface water, Germany	Ternes, 1998
		n/a	0.107	Surface water, U.S. & Canada	Boyd et al., 2003
		0.207	0.551	Surface water, Canada	Metcalfe, Miao et al., 2003
		n/a	0.105	Surface water, U.S.	Gross et al., 2004
		n/a	0.065	Raw drinking water, Canada	Boyd et al., 2003
	Ketoprofen	n/a	0.008	Drinking water, Finland	Vieno et al., 2005
Synthetic Hormones	EE2 (17α-ethinyl-estradiol)	0.029	0.042	Sewage effluent, Canada	Ternes et al., 1999
		<LOQ	0.0043	Surface water, Netherlands	Belfroid et al., 1999
		n/a	0.0046	Surface water, U.K.	Williams, Johnson, Smith, & Kanda, 2003
		0.094[*]	0.273	Surface water, U.S.	Kolpin et al., 2002b
		n/a	0.0024	Groundwater, Germany	Adler, Steger-Hartmann, & Kalbfus, 2001
	Mestranol	0.017	0.407	Surface water, U.S.	Kolpin et al., 2002a
Anti-epileptics	Carbamazepine	n/a	2.3	STP effluent, Canada	Metcalfe, Koenig et al., 2003
		n/a	0.330	Surface water, Germany	Heberer et al., 2004
		0.25	1.1	Surface water, Germany	Ternes, 1998
		0.185	0.650	Surface water, Canada	Metcalfe, Miao et al., 2003
		n/a	1.1	Groundwater, Germany	Ternes, 2001
		n/a	0.070	Groundwater (raw drinking water), Germany	Heberer et al., 2004
		n/a	< 0.70	Drinking water, Canada	Mittelstaedt, 2003
	Primidone	n/a	0.060	Surface water, Germany	Heberer et al., 2004
		n/a	0.040	Groundwater (raw drinking water), Germany	Heberer et al., 2004
SSRIs	Fluoxetine	n/a	0.046	Surface water, Canada	Metcalfe, Miao et al., 2003
		0.012[*]	0.012	Surface water, U.S.	Kolpin et al., 2002a
Cytostatics	Cyclophos-phamide	<LOQ	0.020	STP effluent, Germany	Ternes, 1998
	Ifosfamide	0.0093	0.040	STP effluent, Germany	Kümmerer et al., 1997
X-Ray Agents	Diatrizoate	n/a	1.2	Raw drinking water, Germany	Putschew et al., 2000
	Iopromide	n/a	1.6	Surface water, Germany	Putschew et al., 2000
Beta-Blockers	Sotalol	n/a	0.560	Groundwater, Germany	Sacher et al., 2001
	Metoprolol	0.045	2.2	Surface water, Germany	Ternes, 1998

Table 2.2 cont'd. Occurrence of PhACs in aquatic environments: some findings of note

2.6. Environmental impacts of PhACs

2.6.1. Impacts of PhACs in drinking water on human health

PhACs have been detected in drinking water in Canada (Mittelstaedt, 2003) and other countries (Stan et al., 1994) at ng/L concentrations or lower. However, there is currently no evidence that these levels of PhACs have detrimental effects on human health. Concentrations of PhACs in drinking water are several orders of magnitude below therapeutic doses of pharmaceuticals in humans (Webb et al., 2003). Environmental risk assessments considering endpoints in terms of human health indicate that levels of PhACs in drinking water are unlikely to harm healthy adults (Christensen, 1998; Schulman et al., 2002; Webb et al., 2003). However, a lack of evidence of effects does not constitute a lack of effects, and the possibility of subtle, chronic effects of long-term PhAC consumption cannot be eliminated, nor can the possibility of effects on sensitive sub-populations such as embryos and fetuses (Pomati et al., 2006). Concerns also exist in terms of potential effects of PhACs on people with chemical sensitivities or compromised immune systems, and with regard to the development of antibiotic resistance (Christensen, 1998; Daughton & Ternes, 1999).

2.6.2. Impacts of PhACs in surface water on aquatic organisms

Certain PhACs have been found to affect aquatic organisms at μg/L to ng/L concentrations. A well-known example is the feminization of fish in surface water contaminated by 17α-ethinylestradiol (EE2), the active ingredient in oral contraceptives, from WWTP effluent (Jobling et al., 1998; Larsson et al., 1999; Purdom et al., 1994). Environmental risk assessments for PhACs indicate that several PhACs, including ibuprofen, paracetamol, carbamazepine, gemfibrozil, mefenamic acid, and oxytetracycline, are likely present in some aquatic environments at levels sufficiently high to harm aquatic organisms (Ferrari et al., 2003; Henschel et al., 1997; Jones et al., 2002; Sanderson et al., 2003; Stuer-Lauridsen, Birkved, Hansen, Holten Lützhoft, & Halling-Sorensen, 2000; Tauxe-Wuersch et al., 2005). PhACs can be expected to have effects on aquatic organisms, as they are often highly bioactive even at low concentrations (Purdom et al., 1994), are designed to resist degradation (Stuer-Lauridsen

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et al., 2000), have several target receptors, and follow complex biological pathways (Daughton & Ternes, 1999). Furthermore, the continuous release of PhACs to surface waters means that aquatic organisms are constantly exposed to the contaminants, throughout several life-cycles (Daughton & Ternes, 1999). Not only can PhACs affect vertebrates such as fish, but they have also been found to affect invertebrates in laboratory studies (Brooks et al., 2003; Pascoe, Karntanut, & Müller, 2003); in fact some invertebrates may be more sensitive to PhACs than many vertebrates (Ferrari et al., 2003). Effects on algae (Halling-Sorensen, 2000; Wilson, Smith, Denoyelles, & Larive, 2003) and bacteria (Guardabassi et al., 1998; Kümmerer, Al-Ahmad, & Mersch-Sundermann, 2000; Kümmerer & Henninger, 2003) have been documented as well. PhACs are unlikely to have acute effects, such as fish kills, at most environmental concentrations (Farré et al., 2001; Sanderson et al., 2003). The recent discovery that vultures in Asia have been dying from eating cattle containing relatively low concentrations of the drug diclofenac (Oaks et al., 2004), however, illustrates that acute effects as a result of exposure to relatively low levels of PhACs are possible. Most scientists are concerned about the potential for subtle, long-term, possibly multi-generational effects on aquatic organisms (Daughton & Ternes, 1999; Jones et al., 2002; Jorgensen & Halling-Sorensen, 2000; Stuer-Lauridsen et al., 2000). It is extremely difficult to predict how PhACs might affect non-target organisms (Daughton & Ternes, 1999). Therefore standard acute toxicity tests are likely of limited use in assessing the environmental impacts of PhACs (Ferrari et al., 2003; Länge & Dietrich, 2002; Sanderson et al., 2004; Sanderson et al., 2003). More sophisticated environmental assessment methods are needed, potentially including QSAR modelling (Sanderson et al., 2004; Sanderson et al., 2003), microcosm and mesocosm studies (Brain et al., 2004; Brooks et al., 2003), and methodologies designed to test for endocrine disrupting effects (Environment Canada, 1999; Sutcliffe, 2001; US EPA, 2004).

2.7. Mixture effects

Assessment of the effects of PhACs is complicated by the presence of PhACs – and other compounds – as mixtures in environmental conditions. Environmental contaminants are always present as mixtures, and many substances are subject to mixture

effects. The complex nature of the pharmacodynamic behavior of pharmaceuticals, however, poses a particular challenge and concern (Daughton & Ternes, 1999; Sanderson et al., 2004). For instance, a recent study found that interactions among a mixture of drugs at environmental (ng/L) concentrations caused a reduction in cell proliferation in vitro (Pomati et al., 2006). Cleuvers (2003) found that concentration addition effects occurred when daphnia were exposed to mixtures of clofibric acid and carbamazepine, but independent action was found for algae exposed to the same mixture. Ibuprofen and diclofenac exerted additive effects on both species when mixed. Silva, Rajapakse and Kortenkamp (2003) found that mixtures of xenoestrogens displayed effects according to the concentration addition model. In the concentration addition model, substances present at concentrations below their NOEC (No Observed Effects Concentration) can contribute to a total mixture effect; this is not the case for independent action. As concentration addition appears to be the appropriate model for mixture effects more frequently than independent action, it is likely that many PhACs found in the environment contribute to effects on organisms as part of mixtures, despite being present at concentrations lower than the NOEC for the organism in question.

2.8. Gaps in scientific understanding of PhACs in aquatic environments

2.8.1. Human health effects

While risk assessments suggest that exposure to PhACs at ng/L concentrations in drinking water is unlikely to be detrimental to human health, media reports of pharmaceuticals in water are raising concerns about effects such as endocrine disruption and antibiotic resistance among the public (Brooymans, 2005; Mittelstaedt, 2003). Research confirming that sensitive sub-populations of humans are not at risk is needed. Exposure of prenatal and neonatal babies to PhACs is of particular concern. Recent research has produced evidence that pharmaceutical mixtures at environmental concentrations (ng/L) can affect embryonic cell growth (Pomati et al., 2006). Exposure to hormonally active substances during critical development periods such as adolescence should be considered as well (Barlow et al., 1999; Foster, 2001). Animal studies can be used to give an indication of which substances may have detrimental effects on humans at

low doses, but scientists are rightly cautious about extrapolating from animals to humans (Purchase & Randall, 1998; Slovic et al., 1995). The use of epidemiological data is fraught with difficulties, including the separation of background effects, such as the consumption of PhACs or hormonally active substances in food, from the effects of PhACs in drinking water (Foster, 2001; Webb et al., 2003). Researchers are coming to the realization that for environmental exposure of humans to substances that may interact with hormonal systems, timing may be more important than dose. While not all PhACs are hormonally active, more PhACs may affect hormonal systems than is obvious at first glance. For instance, Trudeau et al. (2004) found that the lipid regulator gemfibrozil reduced testosterone levels in goldfish, likely because the drug affects levels of cholesterol, from which testosterone is manufactured. Human exposure to hormonally active substances during critical windows of growth and development may result in health effects, when at another time exposure to such low levels might not be harmful (Barlow et al., 1999; Daughton & Ternes, 1999; Ibarreta & Swan, 2002). Furthermore, the effects of hormonally active agents on humans may only appear decades, sometimes even generations, after exposure (Ibarreta & Swan, 2002). The potential importance of timing, and the possibility of delayed effects of PhACs on humans, makes the already challenging assessment of effects on humans extremely problematic.

2.8.2. Ecosystem effects

The primary concern with regard to the environmental impacts of PhACs is ecosystem health, rather than human health (Sanderson et al., 2003; Schulman et al., 2002). However, the effects of PhACs on aquatic ecosystems are poorly understood; much more research is needed into this aspect of the problem. Because PhACs can act in a variety of unexpected ways on non-target organisms (Daughton & Ternes, 1999), and because of the complexity of ecosystems, it will be very difficult to predict the ways in which aquatic ecosystems might be affected . Microcosm and mesocosm studies (Brain et al., 2004; Brooks et al., 2003) and laboratory experiments focusing on sub-lethal effects (Trudeau et al., 2004) resulting from low-level, chronic exposure of aquatic organisms to PhACs, preferably over several generations, will be most helpful in this regard (Ferrari et al., 2003). Monitoring of ecosystem health, and of the health of aquatic

organisms, in areas where PhACs are found in the water – in agricultural areas and downstream from WWTP effluent, for instance – will also help to ascertain the effects of PhACs on aquatic organisms (Jobling et al., 1998). It is essential that research into ecosystem effects of PhACs be as anticipatory as possible, so that damage to ecosystems is minimized.

2.8.3. *Effects of mixtures*

The effects of mixtures of environmental contaminants remain poorly understood and require more research. While most risk assessment methods focus on one substance at a time, aquatic organisms inhabiting lakes and streams, and humans consuming groundwater, are exposed to multiple contaminants. Toxicological studies must not only examine the effects of individual PhACs on organisms, but must assess the effects of exposure to several PhACs at once (Cleuvers, 2003) (See Section 2.7 for more detail on possible types of mixture effects).

2.8.4. *Fate and transport*

There is a need to better understand the fate and transport of PhACs, from consumption or initial release to the environment, to their occurrence in surface water, groundwater, and drinking water. Currently analyses of PhACs in WWTP influent and effluent focus mainly on the parent compound; but the occurrence and effects of metabolites must also be considered (Kolpin et al., 2002a; Ternes, 2001). The effects of sewage treatment on PhACs remain poorly understood; in particular the generation of byproducts by treatment methods such as chlorination and ozonation requires research (Boyd et al., 2005; McDowell, Huber, Wagner, Von Gunten, & Ternes, 2005; Snyder et al., 2003; Tabata et al., 2003). The distribution of PhACs in sewage sludge and manure, and the potential for groundwater or surface water contamination as a result of land application of the sludge (biosolids) or manure, must be explored (Colucci & Topp, 2001). Contributions of sources such as septic tanks and leakage from underground sewage pipes and sewer overflows to loadings of PhACs to aquatic environments should also be assessed (Fono & Sedlak, 2005; Hua et al., 2003).

2.9 Priority PhACs

An understanding of fate, transport, and effects can help us to assess which pharmaceuticals may represent the greatest concern in terms of environmental impact. These 'priority PhACs' include the compounds to which aquatic organisms are most likely to be exposed, and which are most likely to have adverse effects on organisms. Table 2.3 presents a rough ranking of some commonly detected PhACs of concern. The ranking is based on scores out of ten for a) persistence during sewage treatment, based on literature values for WWTP removal rates (Table 2.1); b) persistence in the environment, based on half-lives found in the literature (Table 2.1), and c) likelihood of adverse effects on aquatic organisms, based on findings of effects and on risk assessments reported in the peer-reviewed literature. It should be noted, however, that there are many other factors which are also important in determining which contaminants are of more concern than others. For instance, this ranking does not account for the frequency of detection of the PhACs in surface water or groundwater, although those compounds being ranked are those most frequently discussed in the literature. The ranking also does not account for localized use; for example, clofibrate has been used to a greater extent in Europe than in North America; therefore research on clofibric acid may be more important in the EU than in Canada or the U.S. The purpose is not to give an exact, quantitative ranking of risk, but merely to make use of the data and information available in the literature, to provide a general picture of which PhACs may be of greatest concern. A ranking of classes of PhACs and personal care products according to environmental risk, based on QSAR (quantitative structure activity relationship) modelling, can be found in Sanderson et al. (2004). A ranking based on the criteria of persistence, bioaccumulation, and toxicity (PBT) can be found in a booklet published by the Stockholm County Council (Stockholm läns landsting, 2005).

In Table 2.3, the substances having scores of 20 or more, are the 'high priority' PhACs. The ranking suggests that carbamazepine, clofibric acid, ifosfamide, 17α-ethinylestradiol (EE2), oxytetracyline, ciprofloxacin, and diclofenac are 'high priority' substances and therefore merit the greatest research efforts. These substances are very persistent in surface water, aquifers, or soils, are poorly removed by wastewater treatment, and/or have a high potency and potential to affect non-target organisms. The

PhAC	Class	WWTP removal score	Persistence score	Effects score	Total
Carbamazepine	*Anti-epileptic*	*9*	*10*	*6*	*25*
Clofibric acid	*Lipid regulator*	*9*	*10*	*5*	*24*
Ifosfamide	*Cytostatic*	*10*	*4^{*}*	*9*	*23*
17α-ethinylestradiol	*Synthetic hormone*	*5*	*7*	*9*	*21*
Oxytetracycline	*Antimicrobial*	*4^{*}*	*10*	*7*	*21*
Ciprofloxacin	*Antimicrobial*	*2*	*10*	*8*	*20*
Diclofenac	*Analgesic*	*8*	*3*	*9*	*20*
Iopromide	**X-Ray contrast agent**	**10**	**7**	**2**	**19**
Gemfibrozil	**Lipid regulator**	**6**	**4**^{*}	**7**	**17**
Melengesterol Acetate (MGA)	**Synthetic hormone**	**4**^{*}	**9**	**4**^{*}	**17**
Fluoxetine	**SSRI**	**4**^{*}	**4**^{*}	**8**	**16**
Bezafibrate	**Lipid regulator**	**5**	**4**^{*}	**5**	**14**
Ketoprofen	**Analgesic**	**6**	**4**^{*}	**4**^{*}	**14**
Ibuprofen	**Analgesic**	**2**	**7**	**5**	**14**
Ofloxacin	**Antimicrobial**	**4**^{*}	**4**	**6**	**14**
Naproxen	**Analgesic**	**5**	**4**	**4**	**13**
Propranolol	**Beta blocker**	**3**	**5**	**4**^{*}	**12**
Sulfamethoxazole	**Antimicrobial**	**4**	**2**	**6**	**12**
Salicylic acid	Analgesic	1	4^{*}	5	10
Acetominophen	Analgesic	1	4^{*}	4^{*}	9

*A score of 4 was assigned when there was insufficient data or no data.

Table 2.3. Priority ranking of PhACs based on WWTP removal, persistence in the environment, and a qualitative scoring of effect. Values on which scores for WWTP removal and environmental persistence are based can be found in Table 2.1.

substances with rankings from 12-19 are the 'moderate priority' PhACs; they are not top priorities as they are either removed reasonably effectively by WWTPs, degrade relatively quickly in the environment, or have no evidence of detrimental effects; but their removal or degradation is not complete, and they remain a concern. Research on these substances is certainly worth pursuing, although their priority in terms of research effort is lower than for the 'high priority' substances. Lastly, there are the PhACs with total scores of less than 12, identified as 'low priority' substances. These substances are not persistent and are unlikely to be harmful to aquatic organisms; they require a low level of concern. It should be noted that uncertainty remains high with regard to removal, degradation, and especially effects of PhACs, so future findings may change the order of priority with regard to the risks these substances present.

2.10. Conclusions

In recent decades there has been an increase in interest in pharmaceuticals in the environment. As analytical technology has allowed for the detection of lower and lower concentrations of these substances in aquatic systems, their ubiquity in the environment has become apparent. However, the risks that PhACs present to human and ecosystem health, remain unclear. While some PhACs have been found to have subtle, chronic effects on the reproduction, development and/or behavior or aquatic species, much more research on their effects on aquatic organisms and ecosystems is required. At this time, the level of scientific uncertainty with regard to the risks of PhACs in surface water, groundwater, and drinking water, remains high.

2.11. References

Adams, C., Wang, Y., Loftin, K., & Meyer, M. (2002). Removal of antibiotics from surface and distilled water in conventional water treatment process. *Journal of Environmental Engineering, 128*(3), 253-260.

Adler, P., Steger-Hartmann, T., & Kalbfus, W. (2001). Vorkommen naturlicher und synthetischer ostrogener Steroid in Wassern des sud- und mitteldeutschen Raumes (Distribution of natural and synthetic estrogenic steroid hormones in water samples from southern and middle Germany). *Acta hydrochimica hydrobiologia, 29*, 227-241.

Al-Ahmad, A., Daschner, F. D., & Kümmerer, K. (1999). Biodegradability of cefotiam, ciprofloxacin, meropenem, penicillin G., and sulfamethoxazole and inhibition of waste water bacteria. *Archives of Environmental Contamination and Toxicology, 37*(158-163).

Andreozzi, R., Caprio, V., Ciniglia, C., de Champdoré, M., Lo Giudice, R., Marotta, R., et al. (2004). Antibiotics in the environment: occurrence in Italian STPs, fate, and preliminary assessment on algal toxicity of amoxicillin. *Environmental Science and Technology, 38*, 6832-6838.

Andreozzi, R., Raffaele, M., & Nicklas, P. (2003). Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environments. *Chemosphere, 50*, 1319-1330.

Arslan-Alaton, I., & Caglayan, A. E. (2006). Toxicity and biodegradability assessment of raw and ozonated procaine penicillin G formulation effluent. *Ecotoxicology and Environmental Safety, 63*, 131-140.

AstraZeneca. (2003). *Pharmaceuticals in the environment*. Retrieved July 19, 2005, from http://www.astrazeneca.com/article/11343.aspx

Balcýoðlu, I. ý. A., & Ötker, M. (2003). Treatment of pharmaceutical wastewater containing antibiotics by O_3 and O_3/H_2O_2 processes. *Chemosphere, 50*, 85-95.

Barlow, S., Kavlock, R. J., Moore, J. A., Schantz, S. L., Sheehan, D. M., Shuey, D. L., et al. (1999). Teratology Society Public Affairs Committee Position Paper: Developmental Toxicity of Endocrine Disruptors to Humans. *Teratology, 60*, 365-375.

Barnes, K. K., Christenson, S. C., Kolpin, D. W., Focazio, M. J., Furlong, E. T., Zaugg, S. D., et al. (2004). Pharmaceuticals and other organic waste water contaminants within a leachate plume downgradient of a municipal landfill. *Ground Water Monitoring and Remediation, 24*(2), 119-126.

Baronti, C., Curini, R., D'Ascenzo, G., Di Corcia, A., Gentili, A., & Samperi, R. (2000). Monitoring natural and synthetic estrogens at activated sludge sewage treatment plants and in a receiving river water. *Environmental Science and Technology, 34*(24), 5059-5066.

Bedner, M., & MacCrehan, W. A. (2006). Transformation of acetaminophen by chlorination produces the toxicants 1,2-benzoquinone and *N*-acetyl-p-benzoquinone imine. *Environmental Science and Technology, 40*(2), 516-522.

Belfroid, A. C., Van der Horst, A., Vetthak, A. D., Schafer, A. J., Rijs, G., Wegener, J., et al. (1999). Analysis and occurrence of estrogenic hormones and their glucuronides in surface water and waste water in the Netherlands. *Science of the Total Environment, 225*(1-2), 101-108.

Boreen, A., Arnold, W. A., & McNeill, K. (2003). Photodegradation of pharmaceuticals in the aquatic environment: a review. *Aquatic Sciences, 65*, 320-341.

Bound, J. P., & Voulvoulis, N. (2004). Pharmaceuticals in the aquatic environment -- a comparison of risk assessment strategies. *Chemosphere, 56*, 1143-1155.

Boxall, A. B. A., Blackwell, P., Cavallo, R., Kay, P., & Tolls, J. (2002). The sorption and transport of a sulphonamide antibiotic in soil systems. *Toxicology Letters, 131*, 19-28.

Boyd, G. R., Reemtsma, H., Grimm, D. A., & Mitra, S. (2003). Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *The Science of the Total Environment, 311*, 135-149.

Boyd, G. R., Zhang, S., & Grimm, D. A. (2005). Naproxen removal from water by chlorination and biofilm processes. *Water Research, 39*, 668-676.

Brain, R. A., Johnson, D. J., Richards, S. M., Hanson, M. L., Sanderson, H., Lam, M. W., et al. (2004). Microcosm evaluation of the effects of an eight pharmaceutical mixture to the aquatic macrophytes *Lemna gibba* and *Myriophyllum sibiricum*. *Aquatic Toxicology, 70*, 23-40.

Brooks, B. W., Foran, C. M., Richards, S. M., Weston, J., Turner, P. K., Stanley, J. K., et al. (2003). Aquatic ecotoxicology of fluoxetine. *Toxicology Letters, 142*, 169-183.

Brooymans, H. (2005, Tuesday October 25). Alberta rivers a pharmaceutical soup: Could render antibiotics useless, feminize fish in long run. *The Edmonton Journal,* p. A3.

Bund/Länderausschuss für Chemikaliensicherheit (BLAC). (2003). *Arzneimittel in der Umwelt: Auswertung der Untersuchungsergebnisse*. Hamburg: 61st Umweltministerkonferenz.

Buser, H.-R., Poiger, T., & Müller, M. D. (1999). Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. *Environmental Science and Technology, 33*, 2529-2535.

Buser, H.-R., Polger, T., & Müller, M. D. (1998). Occurrence and fate of the pharmaceutical drug diclofenac in surface waters: rapid photodegradation in a lake. *Environmental Science and Technology, 32*, 3449-3456.

Carballa, M., Omil, F., Lema, J. M., Llompart, M., García-Jares, C., Rodríguez, I., et al. (2004). Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. *Water Research, 38*, 2918-2926.

Carlson, J. C., & Mabury, S. A. (2006). Dissipation kinetics and mobility of chlortetracycline, tylosin, and monensin in an agricultural soil in Northumberland County, Ontario, Canada. *Environmental Toxicology and Chemistry, 25*(1), 1-10.

Castiglioni, S., Bagnati, R., Fanelli, R., Pomati, F., Calamari, D., & Zuccato, E. (2006). Removal of pharmaceuticals in sewage treatment plants in Italy. *Environmental Science and Technology, 40*(1), 357-363.

Christensen, F. M. (1998). Pharmaceuticals in the environment -- a human risk? *Regulatory Toxicology and Pharmacology, 28*, 212-221.

Clara, M., Kreuzinger, N., Strenn, B., Gans, O., & Kroiss, H. (2005). The solids retention time -- a suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants. *Water Research, 39*, 97-106.

Clara, M., Strenn, B., & Kreuzinger, N. (2004). Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behavior

of carbamazepine in wastewater treatment and during groundwater infiltration. *Water Research, 38*, 947-954.

Cleuvers, M. (2003). Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. *Toxicology Letters, 142*, 185-194.

Colucci, M. S., & Topp, E. (2001). Persistence of estrogenic hormones in agricultural soils: II. 17α-ethinylestradiol. *Journal of Environmental Quality, 30*, 2077-2080.

Daughton, C. G. (2001). Pharmaceuticals and personal care products in the environment: Overarching issues and overview. In C. G. Daughton & T. L. Jones-Lepp (Eds.), *Pharmaceuticals and personal care products in the environment: Scientific and regulatory issues* (pp. 2-38). Washington: American Chemical Society.

Daughton, C. G. (2004a). Non-regulated water contaminants: emerging research. *Environmental Impact Assessment Review, 24*(7-8), 711-732.

Daughton, C. G. (2004b). PPCPs in the environment: Future research -- beginning with the end always in mind. In K. Kümmerer (Ed.), *Pharmaceuticals in the environment* (2nd ed., pp. 463-495). Berlin: Springer.

Daughton, C. G., & Ternes, T. A. (1999). Pharmaceuticals and personal care products in the environment: Agents of subtle change? *Environmental Health Perspectives, 107*, 907-938.

Dizer, H., Fischer, B., Sepulveda, I., Loffredo, E., Senesi, N., Santana, F., et al. (2002). Estrogenic effect of leachates and soil extracts from lysimeters spiked with sewage sludge and reference endocrine disrupters. *Environmental Toxicology, 17*, 105-112.

Doll, T. E., & Frimmel, F. H. (2003). Fate of pharmaceuticals -- photodegradation by simulated solar UV-light. *Chemosphere, 52*(1757-1769).

Drewes, J. E., Heberer, T., Rauch, T., & Reddersen, K. (2003). Fate of pharmaceuticals during ground water recharge. *Ground Water Monitoring and Remediation, 23*(3), 64-72.

Eckel, W. P., Ross, B., & Isensee, R. K. (1993). Pentobarbital found in ground water. *Ground Water, 31*(5), 801-804.

Eichhorn, P., Ferguson, P. L., Pérez, S., & Aga, D. S. (2005). Application of ion trap-MS with H/D exchange and QqTOF-MS in the identification of microbial degradates

of trimethoprim in nitrifying activated sludge. *Analytical Chemistry, 77*, 4176-4184.

Environment Canada. (1999, 2003-07-29). *Environment Canada's national strategy for addressing endocrine disrupting substances in the environment*. Retrieved February 25, 2004, from http://www.ec.gc.ca/eds.strat_e.htm

Esperanza, M., Suidan, M. T., Wang, Z.-M., & Sorial, G. A. (2004). Determination of sex hormones and nonylphenol ethoxylates in the aqueous matrixes of two pilot-scale municipal wastewater treatment plants. *Environmental Science and Technology, 38*, 3028-3035.

Farré, M., Ferrer, I., Ginebreda, A., Figuera, M., Olivella, L., Tirapu, L., et al. (2001). Determination of drugs in surface water and wastewater samples by liquid chromatography-mass spectrometry: methods and preliminary results including toxicity studies with *Vibrio fischeri. Journal of Chromatography A, 938*, 187-197.

Ferrari, B., Paxeus, N., Lo Giudice, R., Pollio, A., & Garric, J. (2003). Ecotoxicological impact of pharmceuticals found in treated wastewaters: study of carbamazepine, clofibric acid, and diclofenac. *Ecotoxicology and Environmental Safety, 55*, 359-370.

Fong, P. P. (1998). Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. *Biology Bulletin, 194*, 143-149.

Fong, P. P. (2001). Antidepressants in aquatic organisms: a wide range of effects. In C. G. Daughton & T. L. Jones-Lepp (Eds.), *Pharmaceuticals and personal care products in the environment: scientific and regulatory issues* (pp. 264-281). Washington, D.C.: American Chemical Society.

Fono, L. J., & Sedlak, D. L. (2005). Use of the chiral pharmaceutical propranolol to identify sewage discharges into surface waters. *Environmental Science and Technology, 39*(23), 9244-9252.

Foster, W. G. (2001). Endocrine disruption and human reproductive effects: an overview. *Water Quality Research Journal of Canada, 36*(2), 253-271.

Golet, E. M., Xifra, I., Siegrist, H., Alder, A. C., & Giger, W. (2003). Environmental exposure assessment of fluoroquinolone antibacterial agents from sewage to soil. *Environmental Science and Technology, 37*(15), 3243.

Greiner, P., & Rönnefahrt, I. (2003, April 14-16). *Management of environmental risks in the life cycle of pharmaceuticals.* Paper presented at the Envirapharma, Lyon.

Gross, B., Montgomery-Brown, J., Naumann, A., & Reinhard, M. (2004). Occurrence and fate of pharmaceuticals and alkylphenol ethoxylate metabolites in an effluent-dominated river and wetland. *Environmental Toxicology and Chemistry, 23*(9), 2074-2083.

Guardabassi, L., Petersen, A., Olsen, J. E., & Dalsgaard, A. (1998). Antibiotic resistance in acinetobacter spp. isolated from sewers receiving waste effluent from a hospital and a pharmaceutical plant. *Applied and Environmental Microbiology, 64*(9), 3499-3502.

Halling-Sorensen, B. (2000). Algal toxicity of antibacterial agents used in intensive farming. *Chemosphere, 40*, 731-739.

Han, G. H., Hur, H. G., & Kim, S. D. (2006). Ecotoxicological risk of pharmaceuticals from wastewater treatment plants in Korea: Occurrence and toxicity to *Daphnia magna*. *Environmental Toxicology and Chemistry, 25*(1), 265-271.

Hartmann, A., Alder, A. C., Koller, T., & Widmer, R. M. (1998). Identification of fluoroquinolone antibiotics as the main source of *umuC* genotoxicity in native hospital wastewater. *Environmental Toxicology and Chemistry, 17*(3), 377-382.

Heberer, T. (2002a). Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicology Letters, 131*, 5-17.

Heberer, T. (2002b). Tracking persistent pharmaceutical residues from municipal sewage to drinking water. *Journal of Hydrology, 266*, 175-189.

Heberer, T., & Feldmann, D. (2005). Contribution of effluents from hospitals and private households to the total loads of diclofenac and carbamazepine in municipal sewage effluents -- modeling versus measurements. *Journal of Hazardous Materials, 122*, 211-218.

Heberer, T., Feldmann, D., Reddersen, K., Altmann, H., & Zimmerman, T. (2002). Production of drinking water from highly contaminated surface waters: Removal of organic, inorganic, and microbial contaminants applying mobile membrane filtration units. *Acta hydrochimica hydrobiologia, 30*, 24-33.

Heberer, T., Mechlinski, A., Fanck, B., Knappe, A., Massmann, G., Pekdeger, A., et al. (2004). Field studies on the fate and transport of pharmaceutical residues in bank filtration. *Ground Water Monitoring and Remediation, 24*(2), 70-77.

Heberer, T., Schmidt-Bäumier, K., & Stan, H. J. (1998). Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part 1: Drug residues and other polar contaminants in Berlin surface and groundwater. *Acta Hydrochimica Hydrobiologia, 26*(5), 272-278.

Hektoen, H., Berge, J. A., Hormazabal, V., & Yndestad, M. (1995). Persistence of antibacterial agents in marine sediments. *Aquaculture, 133*, 175-184.

Henschel, K.-P., Wenzel, A., Diedrich, M., & Fliedner, A. (1997). Environmental hazard assessment of pharmaceuticals. *Regulatory Toxicology and Pharmacology, 25*, 220-225.

Hirsch, R., Ternes, T., Haberer, K., & Kratz, K.-L. (1999). Occurrence of antibiotics in the aquatic environment. *The Science of the Total Environment, 225*, 109-118.

Holm, J. V., Rugger, K., Bjerg, P. L., & Christensen, T. H. (1995). Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grinsted, Denmark). *Environmental Science and Technology, 29*(5), 1415-1420.

Hua, J., An, P., Winter, J., & Gallert, C. (2003). Elimination of COD, microorganisms and pharmaceuticals from sewage by trickling through sandy soil below leaking sewers. *Water Research, 37*, 4395-4404.

Huber, M. M., Canonica, S., Park, G.-Y., & Von Gunten, U. (2003). Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environmental Science and Technology, 37*(5), 2003.

Ibarreta, D., & Swan, S. H. (2002). The DES story: long-term consequences of prenatal exposure. In S. Guedes Vaz (Ed.), *The precautionary principle in the 20th century* (pp. 90-99). London: Earthscan Publications Ltd.

IMS Health Canada. (2004). *Cholesterol reducers again fastest-growing class among Canada's top prescribed drug classes of 2003[*]*. Retrieved June 11, 2004, from http://www.imshealthcanada.com/htmen/3_1_40.htm

Jobling, S., Nolan, M., Tyler, C. R., Brightly, G., & Sumpter, J. P. (1998). Widespread sexual disruption in wild fish. *Environmental Science and Technology, 32*, 2498-2506.

Johnson, A. C., & Sumpter, J. P. (2001). Removal of endocrine-disrupting chemicals in activated sludge treatment works. *Environmental Science and Technology, 35*(24), 4697-4703.

Jones, O. A. H., Voulvoulis, N., & Lester, J. N. (2002). Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. *Water Research, 36*, 5013-5022.

Jorgensen, S. E., & Halling-Sorensen, B. (2000). Drugs in the environment. *Chemosphere, 40*, 691-699.

Kalsch, W. (1999). Biodegradation of the iodinated X-ray contrast media diatrizoate and iopromide. *The Science of the Total Environment, 225*, 143-153.

Kimura, K., Hara, H., & Watanabe, Y. (2005). Removal of pharmaceutical compounds by submerged membrane bioreactors (MBRs). *Desalination, 178*, 135-140.

Kinney, C. A., Furlong, E. T., Werner, S. L., & Cahill, J. D. (2006). Presence and distribution of wastewater-drived pharmaceuticals in soil irrigated with reclaimed water. *Environmental Toxicology and Chemistry, 25*(2), 317-326.

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, M. E., Zaugg, S. D., Barber, L. B., et al. (2002a). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environmental Science and Technology, 36*, 1202-1211.

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, M. E., Zaugg, S. D., Barber, L. B., et al. (2002b). Response to comment on "Pharmaceuticals, hormones and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance". *Environmental Science and Technology, 36*(18), 4007-4008.

Kümmerer, K. (2001). Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources - a review. *Chemosphere, 45*, 957-969.

Kümmerer, K., Al-Ahmad, A., & Mersch-Sundermann, V. (2000). Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test. *Chemosphere, 40*, 701-710.

Kümmerer, K., & Henninger, A. (2003). Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clinical Microbiology and Infection, 9*, 1203-1214.

Kümmerer, K., Steger-Hartmann, T., & Meyer, M. (1997). Biodegradability of the anti-tumor agent ifosfamide and its occurrence in hospital effluents and communal sewage. *Water Research, 31*(11), 2705-2710.

Länge, R., & Dietrich, D. (2002). Environmental risk assessment of pharmaceutical drug substances -- conceptual considerations. *Toxicology Letters, 131*, 97-104.

Larsson, D. G. J., Adolfsson-Erici, M., Parkkonen, J., Pettersson, M., Berg, A. H., Olsson, P.-E., et al. (1999). Ethinyloestradiol -- an undesired fish contraceptive? *Aquatic Toxicology, 45*, 91-97.

Lee, H.-B., Sarafin, K., Peart, T. E., & Svoboda, M. L. (2004). Acidic pharmaceuticals in sewage -- methodology, stability test, occurrence, and removal from Ontario samples. *Water Quality Research Journal of Canada, 38*(4), 667-682.

Lindberg, R. H., Olofsson, U., Rendahl, P., Johansson, M. I., Ysklind, m., & Andersson, B. A. V. (2006). Behavior of fluoroquinolones and trimethoprim during mechanical, chemical, and active sludge treatment of sewage water and digestion of sludge. *Environmental Science and Technology, 40*(3), 1042-1048.

Lindqvist, N., Tuhkanen, T., & Kronberg, L. (2005). Occurrence of acidic pharmaceuticals in raw and treated sewages and in receiving waters. *Water Research, 39*, 2219-2228.

Löffler, D., Römbke, J., Meller, M., & Ternes, T. A. (2005). Environmental fate of pharmaceuticals in water-sediment systems. *Environmental Science and Technology, 39*(14), 5209-5218.

Loraine, G. A., & Pettigrove, M. E. (2006). Seasonal variations in concentratiosn of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in southern California. *Environmental Science and Technology, 40*(3), 687-695.

Lorenzen, A., Burnison, K., Servos, M., & Topp, E. (2003, April 24 and 25). *Persistence of endocrine-disrupting chemicals in agricultural soils.* Paper presented at the 2nd Canadian Organic Residuals Recycling Conference, Penticton, BC.

Lorphensri, O., Intravijit, J., Sabatini, D. A., Kibbey, T. C. G., Osathaphan, K., & Saiwan, C. (2006). Sorption of acetaminophen, 17α-ethynyl estradiol, nadilixic acid, and norfloxacin to silica, alumina, and a hydrophobic medium. *Water Research, 40*, 1481-1491.

McDowell, D., Huber, M. M., Wagner, M., Von Gunten, U., & Ternes, T. A. (2005). Ozonation of carbamazepine in drinking water: identification and kinetic study of major oxidation products. *Environmental Science and Technology, 39*, 8014-8022.

Metcalfe, C. D., Koenig, B. G., Bennie, D. T., Servos, M., Ternes, T. A., & Hirsch, R. (2003). Occurrence of neutral and acidic drugs in the effluents of Canadian sewage treatment plants. *Environmental Toxicology and Chemistry, 22*(12), 2872-2880.

Metcalfe, C. D., Miao, X.-S., Koenig, B., & Struger, J. (2003). Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada. *Environmental Toxicology and Chemistry, 22*(12), 2881-2889.

Mittelstaedt, M. (2003). Drug traces found in cities' water. *The Globe and Mail, February 10,* p. 1.

Oaks, J. L., Gilbert, M., Virani, M., Watson, R. T., Meteyer, C. U., Rideout, B. A., et al. (2004). Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature, 427*, 630-633.

Packer, J. L., Werner, J. J., Latch, D. E., McNeill, K., & Arnold, W. A. (2003). Photochemical fate of pharmaceuticals in the environment: naproxen, diclofenac, clofibric acid, and ibuprofen. *Aquatic Sciences, 65*, 342-351.

Pascoe, D., Karntanut, W., & Müller, C. T. (2003). Do pharmaceuticals affect freshwater invertebrates? A study with the cnidarian *Hydra vulgaris. Chemosphere, 51*(521-528).

Pomati, F., Castiglioni, S., Zuccato, E., Fanelli, R., Vigetti, D., Rossetti, C., et al. (2006). Effects of a complex mixture of therapeutic drugs at environmental levels on human embryonic cells. *Environmental Science and Technology, 40*, 2442-2447.

Purchase, I. F. H., & Randall, G. L. P. (1998). Natural and anthropogenic environmental oestrogens: the scientific basis for risk assessment: principles of risk assessment. *Pure and Applied Chemistry, 70*(9), 1671-1683.

Purdom, C. E., Hardiman, P. A., Bye, V. J., Eno, N. C., Tyler, C. R., & Sumpter, J. R. (1994). Estrogenic effects of effluents from sewage treatment works. *Chemical Ecology, 8*, 275-285.

Putschew, A., Wischnack, S., & Jekel, M. (2000). Occurrence of triiodinated X-ray contrast agents in the aquatic environment. *Science of the Total Environment, 255*, 129-134.

Reddersen, K., Heberer, T., & Dünnbier, U. (2002). Identification and significance of phenazone drugs and their metabolites in ground- and drinking water. *Chemosphere, 49*, 539-544.

Richardson, M. L., & Bowron, J. M. (1985). The fate of pharmaceutical chemicals in the aquatic environment. *Journal of Pharmacy and Pharmacology, 37*, 1-12.

Sacher, F., Lange, F. T., Brauch, H.-J., & Blankenhorn, I. (2001). Pharmaceuticals in groundwaters. Analytical methods and results of a monitoring program in Baden-Wurtemburg, Germany. *Journal of Chromatography A, 938*, 199-210.

Sanderson, H., Johnson, D. J., Reitsma, T., Brain, R. A., Wilson, C. J., & Solomon, K. R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology, 39*, 158-183.

Sanderson, H., Johnson, D. J., Wilson, C. J., Brain, R. A., & Solomon, K. R. (2003). Probabilistic hazards assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids and algae by ECOSARS screening. *Toxicology Letters, 144*(3), 383-395.

Scheytt, T., Mersmann, P., Leidig, M., Pekdeger, A., & Heberer, T. (2004). Transport of pharmaceutically active compounds in saturated laboratory columns. *Ground Water, 42*(5), 767-773.

Scheytt, T., Mersmann, P., Lindstädt, R., & Heberer, T. (2005). Determination of sorption coefficients of pharmaceutically active substances carbamazepine, diclofenac, and ibuprofen, in sandy sediments. *Chemosphere, 60*, 245-253.

Scheytt, T. J., Mersmann, P., & Heberer, T. (2006). Mobility of pharmaceuticals carbamazepine, diclofenac, ibuprofen, and propyphenazone in miscible-displacement experiments. *Journal of Contaminant Hydrology, 83*, 53-69.

Schiffer, B., Daxenberger, A., Meyer, K., & Meyer, H. H. D. (2001). The fate of trenbolone acetate and melengestrol acetate after application as growth promoters in cattle: environmental studies. *Environmental Health Perspectives, 109*(11), 1145-1151.

Schulman, L. J., Sargent, E. V., Naumann, B. D., Faria, E. C., Dolan, D. G., & Wargo, J. P. (2002). A human health risk assessment of pharmaceuticals in the aquatic environment. *Human and Ecological Risk Assessment, 8*(4), 657-680.

Sedlak, D. L., & Pinkston, K. E. (2001). Factors affecting the concentrations of pharmaceuticals released to the aquatic environment. *Water Resources Update, 120*, 56-64.

Silva, E., Rajapakse, N., & Kortenkamp, A. (2003). Something from "nothing" -- eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environmental Science and Technology, 36*, 1751-1756.

Slovic, P., Malmfors, T., Krewski, D., Mertz, C. K., Neil, N., & Bartlett, S. (1995). Intuitive toxicology. II. Expert and lay judgmenets of chemical risks in Canada. *Risk Analysis, 15*(6), 661-675.

Snyder, S. A., Westerhoff, P., Yoon, Y., & Sedlak, D. L. (2003). Pharmaceuticals, personal care products, and endocrine disruptors in water: implications for the water industry. *Environmental Engineering Science, 20*(5).

Stan, H. J., & Heberer, T. (1997). Pharmaceuticals in the aquatic environment. *Analusis, 25*, M20-M23.

Stan, H. J., Heberer, T., & Linkerhagner, M. (1994). Vorkommen von Clofibrinsaure im aquatischen System -- Fuhrt die therapeutische Anwendung zu einer Belastung von Oberflachen-, Grund- und Trinkwasser? *Vom Vasser, 79*, 57-68.

Steger-Hartmann, T., Länge, R., & Schweinfurth, H. (1999). Environmental risk assessment for the widely used iodinated X-ray contrast agent Iopromide (Ultravist). *Ecotoxicology and Environmental Safety, 42*, 274-281.

Stockholm läns landsting. (2005). *Environmentally classified pharmaceuticals*. Stockholm.

Stuer-Lauridsen, F., Birkved, M., Hansen, L. P., Holten Lützhoft, H.-C., & Halling-Sorensen, B. (2000). Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere, 40*, 783-793.

Stumpf, M., Ternes, T. A., Wilken, R.-D., Rodrigues, S. V., & Baumann, W. (1999). Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. *The Science of the Total Environment, 225*, 135-141.

Sutcliffe, R. (2001). Endocrine disrupting substances and ecological risk assessment of commercial chemicals in Canada. *Water Quality Research Journal of Canada, 36*(2), 303-317.

Tabak, H. H., & Brunch, R. L. (1970). Steroid hormones as water pollutants I. Metabolism of natural and synthetic ovulation inhibiting hormones by micro-organisms of activated sludge and primary settled sludges. *Developments in Industrial Microbiology, 11*, 367-376.

Tabata, A., Miyamoto, N., Itoh, M., Yamada, T., Kamei, T., & Magara, Y. (2003). The effect of chlorination of estrogenic chemicals on the level of serum vitellogenin of Japanese medaka (*Oryzias latipes*). *Water Science and Technology, 47*(9), 51-57.

Taro, U., & Kikuta, T. (2005). Separate estimation of adsorption and degradation of pharmaceutical substances and estrogens in the activated sludge process. *Water Research, 39*, 1289-1300.

Tauxe-Wuersch, A., De Alencastro, L. F., Grandjean, D., & Tarradellas, J. (2005). Occurrence of several acidic drugs in sewage treatment plants in Switzerland and risk assessment. *Water Research, 39*, 1761-1772.

Ternes, T. A. (1998). Occurrence of drugs in German sewage treatment plants and rivers. *Water Research, 32*(11), 3245-3260.

Ternes, T. A. (2001). Pharmaceuticals and metabolites as contaminants of the aquatic environment. In C. G. Daughton & T. L. Jones-Lepp (Eds.), *Pharmaceuticals and*

personal care products in the environment: Scientific and regulatory issues (pp. 39-54). Washington: American Chemical Society.

Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M., et al. (2003). Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Research, 37*, 1976-1982.

Ternes, T. A., Stumpf, M., Mueller, J., Haberer, K., Wilken, R.-D., & Servos, M. (1999). Behavior and occurrenc of estrogens in municipal sewage treatment plans -- I. Investigations in Germany, Canada, and Brazil. *The Science of the Total Environment, 225*, 81-90.

Till, A. (2003). Comment" on "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environmental Science and Technology, 37*(5), 1052-1053.

Tixier, C., Singer, H. P., Oellers, S., & Müller, S. R. (2003). Occurrence and fate of carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen, and naproxen in surface waters. *Environmental Science and Technology, 37*(6), 1061-1068.

Toze, S. (2006). Reuse of water efflunet -- benefits and risks. *Agricultural Water Management, 80*, 147-159.

Trudeau, V., Woodhouse, M., Mimeault, C., Marlatt, V., Liu, G., Gallant, N., et al. (2004, May 17-20). *Fish, frogs and pharmaceuticas: the dangerous environmental cocktail.* Paper presented at the Enviroanalysis, Toronto.

US EPA. (2004). *Endocrine disruptor screening program*. Retrieved February 25, 2004, from http://www.epa.gov/scipoly/oscpendo/

Vieno, N. M., Tuhkanen, T., & Kronberg, L. (2005). Seasonal variation in the occurrence of pharmaceuticals in effluents from a sewage treatment plant and in the recipient water. *Environmental Science and Technology, 39*(21), 8220-8226.

Webb, S., Ternes, T. A., Gibert, M., & Olejniczak, K. (2003). Indirect human exposure to pharmaceuticals via drinking water. *Toxicology Letters, 142*, 157-167.

Weigel, S., Berger, U., Jensen, E., Kallenborn, R., Thoresen, H., & Hühnerfuss, H. (2004). Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. *Chemosphere, 56*, 583-592.

Westerhoff, P., Yoon, Y., Snyder, S. A., & Wert, E. (2005). Fate of endocrine-disruptors, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. *Environmental Science and Technology, 39*(17), 6649-6663.

Wiegel, S., Aulinger, A., Brockmeyer, R., Harms, H., Löffler, J., Reincke, H., et al. (2004). Pharmaceuticals in the river Elbe and its tributaries. *Chemosphere, 57*, 107-126.

Williams, R. J., Johnson, A. C., Smith, J. J. L., & Kanda, R. (2003). Steroid estrogens profiles along river stretches arising from sewage treatment works discharges. *Environmental Science and Technology, 37*, 1744-1750.

Wilson, B. A., Smith, V. H., Denoyelles, F. J., & Larive, C. K. (2003). Effects of three pharmaceutical and personal care products on natural freshwater algal assemblages. *Environmental Science and Technology, 37*, 1713-1719.

Winkler, M., Lawrence, J. R., & Neu, T. R. (2001). Selective degradation of ibuprofen and clofibric acid in two model river biofilm systems. *Water Research, 35*(13), 3197-3205.

Witte, W. (2000). Ecological impact of antibiotic use in animals on different complex microflora: environment. *International Journal of Antimicrobial Agents, 14*, 321-325.

Wolf, L., Held, I., Eiswirth, M., & Hötzl, H. (2004). Impact of leaky sewers on groundwater quality. *Acta hydrochimica hydrobiologia, 32*(4-5), 361-373.

Wollenberger, L., Halling-Sorensen, B., & Kusk, K. O. (2000). Acute and chronic toxicity of veterinary antibiotics to Daphnia magna. *Chemosphere, 40*, 723-730.

Ying, G.-G., Kookana, R. S., & Dillon, P. (2003). Sorption and degradation of selected five endocrine disrupting chemicals in aquifer material. *Water Research, 37*, 3785-3791.

Ying, G.-G., Kookana, R. S., & Dillon, P. (2004). Attenuation of two estrogen compounds in aquifer material supplemented with sewage effluent. *Ground Water Monitoring and Remediation, 24*(2), 102-107.

Ying, G.-G., Kookana, R. S., & Ru, Y.-J. (2002). Occurrence and fate of hormone steroids in the environment. *Environment International, 28*, 545-551.

Yoon, Y., Westerhoff, P., Snyder, S. A., & Wert, E. C. (2006). Nanofiltration and ultrafiltration of endocrine disrupting compounds, pharmaceuticals and personal care products. *Journal of Membrane Science, 270*, 88-100.

Zuccato, E., Calamari, D., Natangelo, M., & Fanelli, R. (2000). Presence of therapeutic drugs in the environment. *The Lancet, 355*, 1789-1790.

Zuelke, S., Duennbier, U., Heberer, T., & Fritz, B. (2004). Analysis of endocrine disrupting steroids: investigation of their release into the environment and their behavior during bank filtration. *Ground Water Monitoring and Remediation, 24*(2), 78-85.

Zwiener, C., & Frimmel, F. H. (2000). Oxidative treatment of pharmaceuticals in water. *Water Research, 34*, 1881-1885.

Chapter 3: Framework and theoretical background for the management of PhACs in the environment

3.1. Introduction

The issue of PhACs in the environment is essentially a question of risk to the health of aquatic organisms, ecosystems, and humans. Therefore, the management of PhACs should ideally be addressed within a risk management framework. However, given the high level of uncertainty currently associated with the effects of PhACs (see Ch. 2), risk management will have to be applied flexibly, foregoing some of the quantitative analysis typically involved. Other planning and management theories must be integrated with risk management to lend the framework the flexibility to deal with uncertainty. The precautionary principle (CEPA, 1999; Quijano, 2003; Rogers, 2001; United Nations General Assembly, 1992) and the theory of adaptive planning (Briassoulis, 1989; Holling, 1978; Lessard, 1998) are particularly appropriate for coping with uncertainty. This chapter discusses how a risk management framework can be modified, using the precautionary principle and adaptive planning, to function under conditions of high uncertainty. The framework developed will provide a basis, in a broad sense, for discussions of risk management throughout the remainder of the thesis.

3.2 Key concepts

The concepts of risk, uncertainty, and the nature of risk management, are central to this chapter, therefore merit some detailed elaboration:

3.2.1. What is risk?

The term 'risk' is subject to much debate in the academic community, particularly between natural scientists and social scientists, and merits clarification here. The more common definition of risk is the positivistic definition, used by scientists and engineers: risk is operationally defined as "the chance of injury or loss as defined as measure of the probability and severity of an adverse effect to health, property, the environment, or other things of value." (Canadian Standards Association, 1997, p. 3). Risk is the product of the probability of exposure and the severity of consequences (McColl, Hicks, Craig, &

Shortreed, 2000). Many social scientists and social theorists, however, question this positivistic definition of risk, pointing out that risk is socially constructed, and can always only be subjectively perceived, not objectively evaluated (Beck, 1992; Covello, 1989; Slovic, 2001). Therefore, they argue that 'perceived risk' or 'risk perception', and 'risk', are one and the same. For example, Beck (1992) states, "*Risk* may be defined as a *systematic way of dealing with hazards and insecurities induced and introduced by modernization itself*." (p. 21), and, "Because risks are risks in knowledge, perceptions of risks and risks are not different things, but one and the same." (p. 55). In this thesis, the term 'risk' refers to the positivistic definition of risk, whereas 'risk perception' or 'perceived risk' will be used to refer to a normative definition of risk. This is not to suggest that risk can be objectively measured or calculated, nor to undermine the importance of values and other normative considerations in decisions regarding risk; on the contrary, these are essential to good risk management. The purpose is simply to make readers aware of the discussion surrounding the term 'risk', and to clarify its use in this dissertation.

3.2.2. What is uncertainty?

Another term essential to the management of PhACs in the environment, which requires some clarification, is the term 'uncertainty'. This term appears to have no unique definition, as it has different meanings according to various authors. According to Hrudey, (1996) uncertainty is comprised of true uncertainty, which is theoretically (although often not practically) reducible, and variability or indeterminacy, which is inherent in natural systems and cannot be reduced. Stirling (2001) defines uncertainty as follows: "Uncertainty...applies to a condition under which there is confidence in the completeness of the defined set of outcomes, but where there is acknowledged to exist no uniquely valid theoretical or empirical basis for the assigning of probabilities of these outcomes." (p. 78), distinguishing it from ignorance: "Ignorance...applies in circumstances where there not only exists no basis for the assigning of probabilities (as under uncertainty), but where the definition of a complete set of outcomes is also problematic. In short, it is an acknowledgement of the possibility of surprises." (p. 78). Rogers (2003) distinguished uncertainty from ignorance by stating that ignorance exists

when relationships between hazard and harm are postulated based on intuition; in the case of uncertainty, there is scientific knowledge or evidence on which these relationships can be based. For the purpose of simplicity, in this thesis, 'uncertainty' will refer to Hrudey's (1996) definition of true uncertainty; the term 'uncertainty' will include both ignorance and uncertainty as defined by Stirling (2001) and Rogers (2003).

3.2.3 What is risk management?

Risk management, in an environmental context, and in its broad sense, can be defined as the process through which decisions regarding the mitigation of risks to the environment are made. Ruckelhaus (1990) describes risk management as follows: "Risk management in its broadest sense means adjusting our environmental policies to obtain the array of social goods – environmental, health-related, social, economic, and psychological – that forms our vision of how we want the world to be." (p. 113). Risk management involves integrating information such as the results of risk analyses, other scientific data about environmental and health impacts, societal concerns, perceptions and public values, financial costs of risks and risk mitigating actions, etc., and balancing these factors so as to yield an optimal decision on how to act (in other words, which policy to implement) faced with a risk (McColl et al., 2000). The purpose of risk management is to identify risks and to take appropriate and reasonable action to minimize these risks, including communicating with stakeholders on the nature of the risks (Canadian Standards Association, 1997).

3.3 Components of risk management

Although different risk management frameworks exist, they all have a number of elements in common. They include, toward the beginning of the risk management process, a scientific assessment or analysis of the risk (Figs. 3.1 & 3.2). For environmental contaminants, the scientific analysis or assessment of risk includes a step where a hazard is identified, based on the physico-chemical properties of a contaminant, its known toxicological effects, and other scientific data. Furthermore, a scientific analysis of risk includes an assessment of the relationship between dose or exposure and
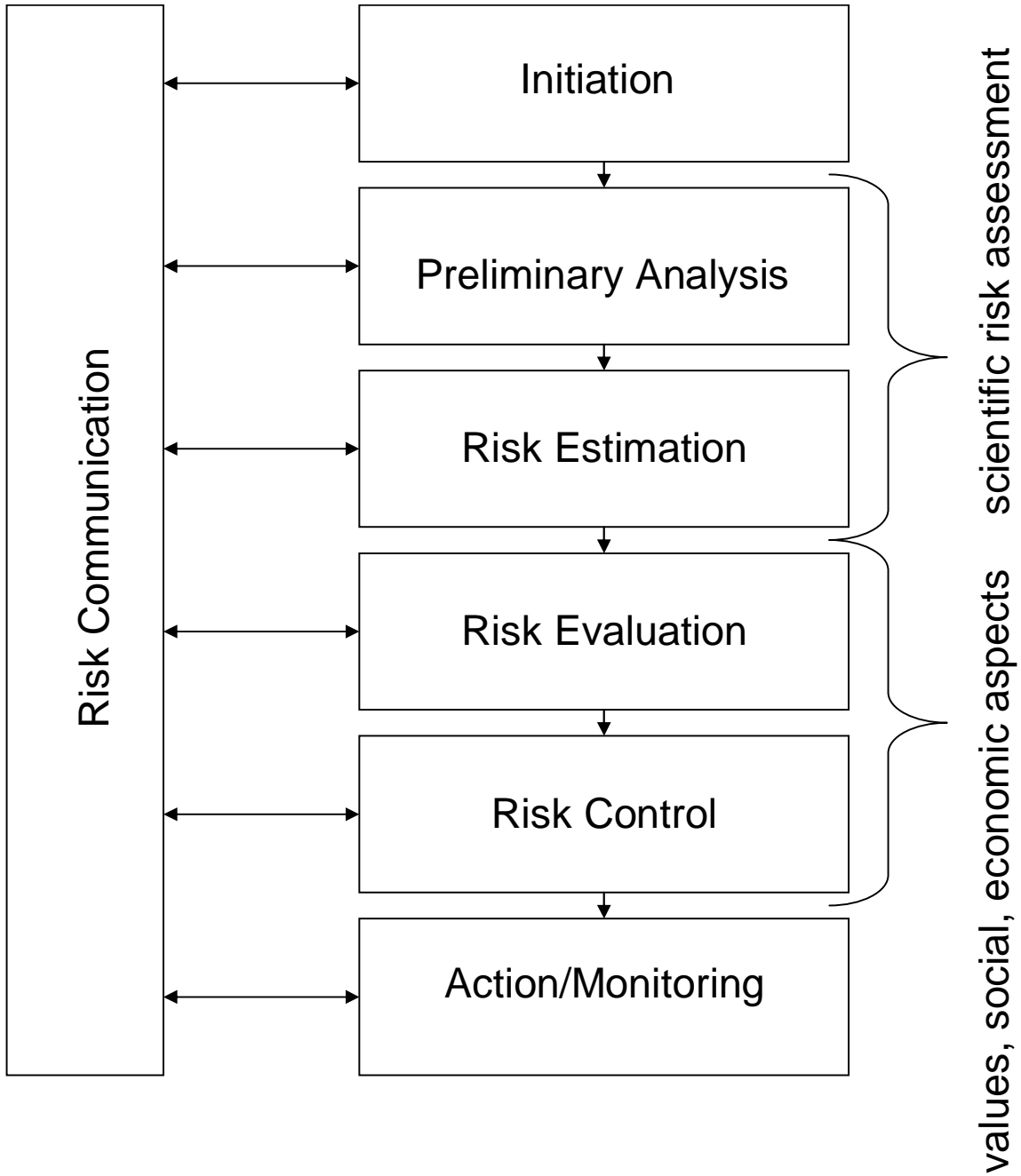
Figure 3.1. Canadian Standards Association risk management framework (1997)(Note: the risk management is meant to be iterative, although the diagram does not show this).
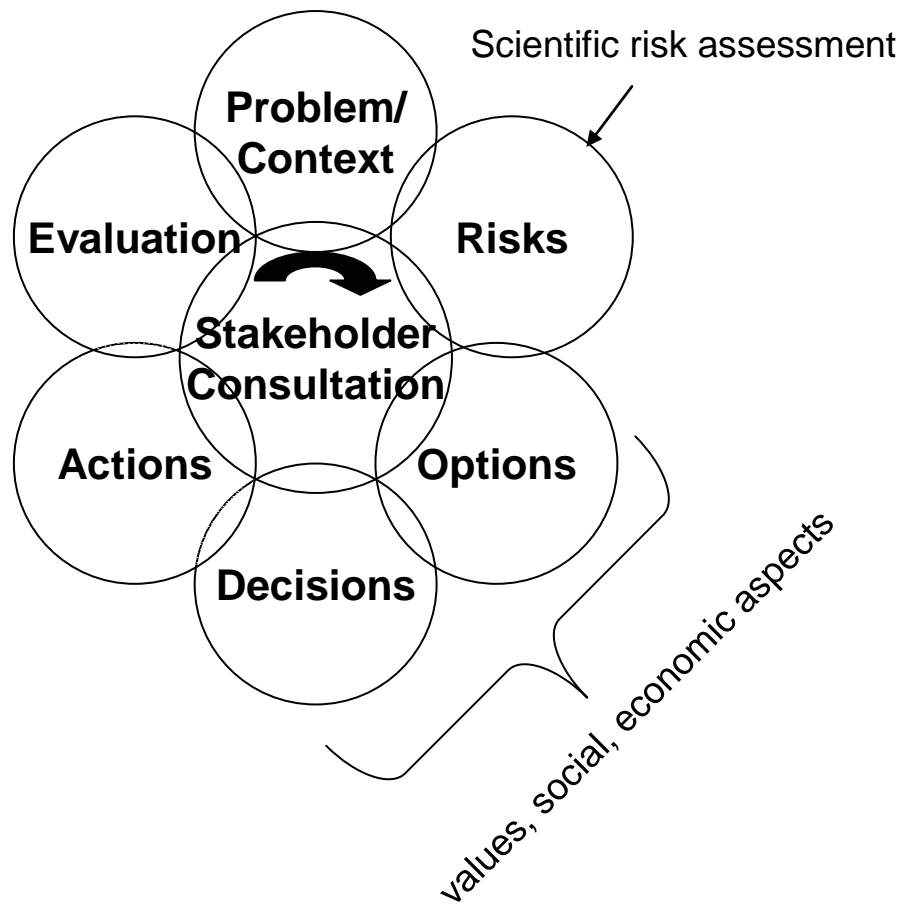
Figure 3.2. Risk management framework from the U.S. Presidential/Congressional Commission on Risk Assessment and Management (1997).

adverse effects, an assessment of exposure of humans or other organisms to the contaminant, and characterization of the risk. Traditionally, risk characterization has referred to a probabilistic estimation of risk (Canadian Standards Association, 1997; McColl et al., 2000). In other words, risk in its positivistic sense is the focus of this first component of risk management.

A second component of risk management goes beyond a scientific analysis of risk to include an assessment of social and economic factors and consultation with stakeholders (Figs. 3.1 & 3.2). The steps in this second portion include, as a minimum, the development of management options; consultation with stakeholders; the evaluation of options based on social, economic, scientific and other information; and a decision as to which management option is to be implemented (Canadian Standards Association, 1997; Health Canada, 1998; The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). In the past, communication and consultation with stakeholders, and social aspects of risks, where perhaps undervalued (Fig. 3.3) (National Research Council, 1983). However these elements now have a much more prominent role in risk management frameworks (Figs. 3.1 & 3.2) (Canadian Standards Association, 1997; The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). It is in this component of the risk management framework that risk perceptions come into play.
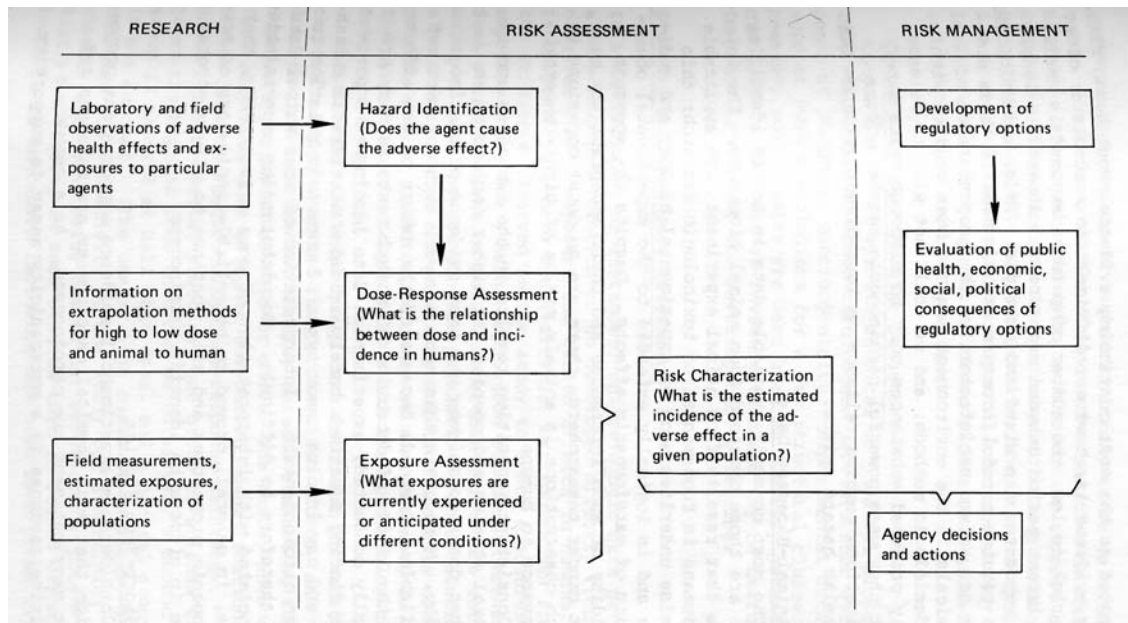
Figure 3.3. National Research Council risk management framework (1983, p. 21)

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3.4. Risk communication: addressing perceptions of risk

Risk perceptions are "intuitive risk judgments" (Slovic, 1987, p. 280), or impressions people have about the nature and magnitude of risks (Leiss & Chociolko, 1994). Public risk perceptions are normative and value-based (Slovic, 1993), and as such they often differ from expert judgments of risk, which are meant to be positivistic and purely scientifically based. Scientific assessments, however, are known also to be based in value judgment (Hood et al., 1992; Turner, 1994), including the valuation of science for its own sake (Beck, 1992). Characterization of lay risk perceptions as incorrect and irrational and expert judgments as correct and rational, however, is misguided (Leiss & Chociolko, 1994; Weterings & Van Eijndhoven, 1989). Lay perceptions of risk often have roots in concepts such as fairness, equity, controllability, and the distribution of risk (Renn, 2004; Slovic, 2001). Slovic (1987) points out, "There is wisdom as well as error in public attitudes and perceptions. Lay people sometimes lack certain information about hazards. However, their basic conceptualization of risk is much richer than that of the experts and reflects legitimate concerns that are typically omitted from expert risk assessments." (p. 285). And Covello (1989) states, "there are multiple truths about risk, and multiple ways of seeing, perceiving and interpreting risk events." (p. 12). The best risk management outcomes will result when both scientific and intuitive assessments of risk are valued, and are used in a complementary fashion in decision making (Healey, 2001; Renn, 2004).

The purpose of risk communication, therefore, should not be to diffuse public concerns or to 'educate' an ignorant public (Covello, 1989); in fact attempts to alleviate public fears through 'education' about the low risk of nuclear energy failed drastically in Canada, heightening fears rather than calming them (Somers, 1995). Risk communication must aim to produce a thoughtful, involved, informed and collaborative public (Covello, 1989). This requires a strong effort to provide for public participation at all stages of risk-related decision making (Renn, 2004; Slovic, 2001; Weterings & Van Eijndhoven, 1989). Furthermore, to allow for collaboration, and to avoid amplifying risk perceptions, trust and confidence in public officials is needed (Covello, 1989; Slovic, 1993). To maintain the public's trust and confidence, governments need to have open, honest, two-way communication with the public and other stakeholders about risk

(Covello, 1989; Hance, Chess, & Sandman, 1989). Value-based concerns must be acknowledged, not dismissed (Healey, 2001; Renn, 2004); and the use of technical jargon must be limited, as it can create suspicion (Covello, 1989; Jardine & Hrudey, 1997; Weterings & Van Eijndhoven, 1989). The public must be informed about health and environmental risks, including the scientific uncertainty surrounding them, as governments learn about them; withholding information will only generate mistrust when the public becomes aware of the risks (Hance et al., 1989). This is of particular importance with respect to PhACs in the environment, as there have been suggestions that the public should not be informed of the issue because of the high level of uncertainty surrounding it (Aumonier, 2003). Such suggestions are misguided. As media reportings of PhACs in the environment continue to emerge (Brooymans, 2005; Mittelstaedt, 2003), it will be essential for governments and industry to discuss the issue, and the uncertainty surrounding it, in a straightforward fashion with the public, and to avoid making trust-destroying mistakes such as the withholding of information.

3.5. Dealing with uncertainty

Uncertainty can present a challenge, not only during risk communication, but also during risk assessment, as is the case for PhACs. As discussed in Chapter 2, traditional risk assessment methods are not appropriate for the detection of the effects of PhACs in the environment (Länge & Dietrich, 2002; Sanderson et al., 2004); as a result, little information, and nearly no reliable quantitative or probabilistic information, is available concerning exposure-effect relationships for PhACs. However, field and laboratory evidence (Fong, 1998; Jobling, Nolan, Tyler, Brightly, & Sumpter, 1998), as well as scientifically-based intuitive reasoning (Daughton & Ternes, 1999), do suggest that PhACs may have detrimental effects on some aquatic species. As Cairns (1999) points out, "Unrecognized risks are still risks; uncertain risks are still risks; and denied risks are still risks." (p. A56). Therefore, it is essential that the risk management process not be brought to a halt by the existence of uncertainty, or the difficulty of quantification. The risk management framework must be modified with a tool for addressing uncertainty and allowing environmental decision-making to continue.

3.6. The precautionary principle

The precautionary principle is a decision making tool meant to guide society towards a sustainable future, in the face of scientific uncertainty. The principle fills the void left in the risk management framework when risk analysis produces uncertain results (Fig. 3.4). Essentially, it states that where some evidence of the potential for harm to the environment or human health exists, scientific uncertainty in causal relationships or other aspects of the risk should not be allowed to delay risk management (Government of Canada, 2001; Harremöes et al., 2002; Quijano, 2003). Implicit in the precautionary principle is the concept that deciding to do nothing -- to maintain the status quo -- *is* a policy decision, and that a decision to do nothing should be considered and reviewed as carefully and as skeptically as a decision to mitigate risk (Santillo, Stringer, Johnston, & Tickner, 1998). There is no single, universal definition of the precautionary principle, but the best known definition is likely the following: "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." (United Nations General Assembly, 1992, Principle 15, p. 4). A definition with less emphasis on the irreversibility of damage or the cost-effectiveness of risk management action was developed at the Wingspread Conference (Wingspread Conference on the Precautionary Principle, 1998): "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically." (p. 2). The precautionary principle originated with the *Vorsorgeprinzip*, or principle of forecaring, which was born out of a concern with growing environmental problems in 1970s Germany. It has since grown and has been referred to in several international agreements such as the North Sea Agreement (Dratwa, 2002), and it is part of the Canadian Environmental Protection Act (CEPA, 1999).

The precautionary principle has a number of elements at is core: 1) prevention of harm is preferable to remediation (Kriebel et al., 2001; Quijano, 2003), 2) a lack of scientific certainty (Government of Canada, 2001; McGarvin, 2001; Quijano, 2003; Rogers, 2001), 3) some evidence suggesting a potential for harm (deFur & Kaszuba,

Risk management
process

Problems

Risk
assessment

Options | Decisions

a)

Risk management
process

Problems | Options | Decisions

Precautionary
Principle

b)
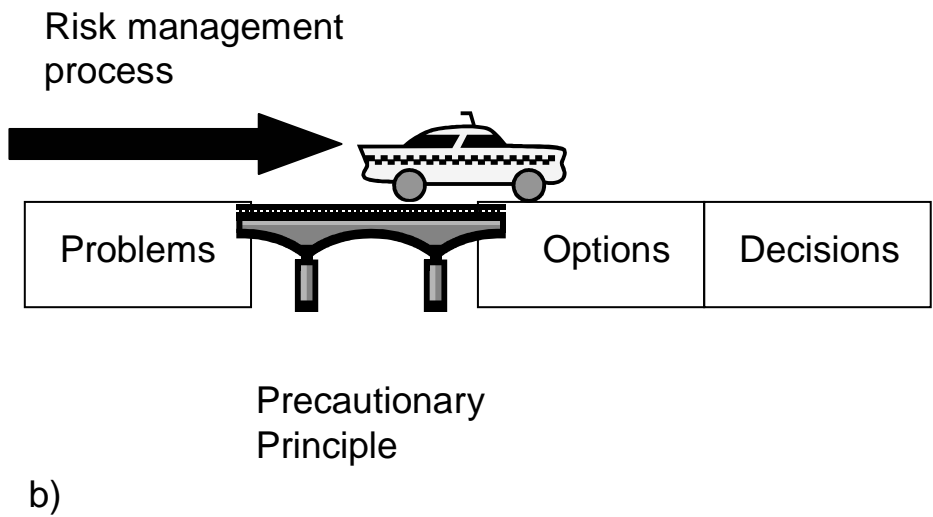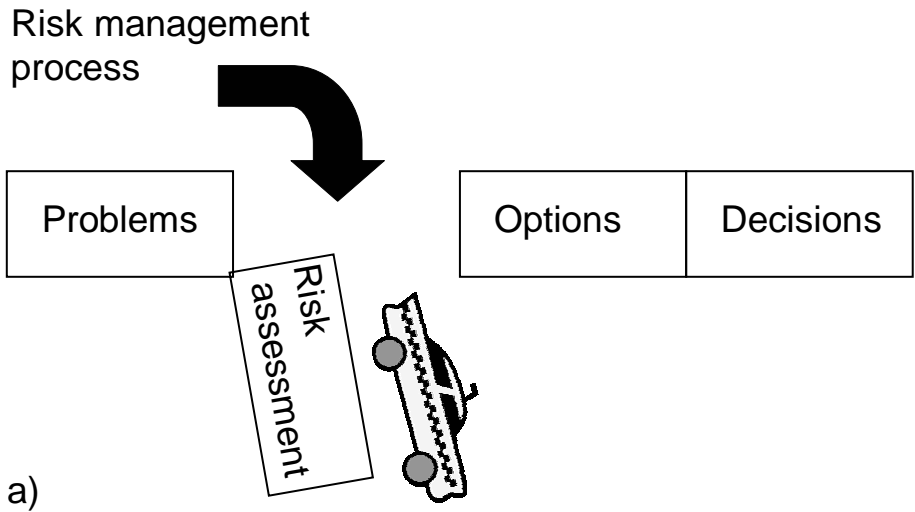
Figure 3.4. a) Without the precautionary principle, the risk management process may
impeded by the inability to conduct a sound, quantitative risk assessment.
b) The precautionary principle fills the gap in risk management when quantitative risk
assessment is not possible.

2002; Government of Canada, 2003; Quijano, 2003), 4) duty to act (deFur & Kaszuba, 2002; Government of Canada, 2003; Santillo et al., 1998), 5) the burden of providing evidence of lack of harm falls on the proponent of an action (Government of Canada, 2003; Jordan & O' Riordan, 1999; Kriebel et al., 2001; Quijano, 2003), 6) need to consider a range of alternative solutions to the problem (Kriebel et al., 2001; Quijano, 2003), 7) importance of public participation (Kriebel et al., 2001; O' Riordan, 2001; O' Riordan, Jordan, & Cameron, 2001; Stirling, 2001), and 8) openness and availability of information (Quijano, 2003).

The first four elements express the central concept of precaution; that evidence of harm, however limited and uncertain, demands some form of mitigative action. Evidence does exist that PhACs in the environment may have detrimental effects on aquatic organisms. This evidence is not sufficient to meet the requirement for probabilistic calculation of risk or construction of exposure-effect curves required in formal, quantitative risk assessment. If traditional, acute risk assessments were used, it would likely be found that PhACs at environmental concentrations do not affect aquatic species (Henschel, Wenzel, Diedrich, & Fliedner, 1997); alternatively it would be necessary to delay risk management until the proper risk assessment methodology for the detection of the subtle, chronic effects of PhACs was developed.   However, applying the precautionary principle allows for the use of whatever limited evidence of environmental impacts exists as a basis for risk management, including qualitative assessments of risk (Commission of the European Communities, 2000). The precautionary principle is therefore an essential component of the risk management process for PhACs in the environment.

The seventh and eight elements listed above, public participation and transparency and honesty, while not central to the precautionary principle as it was originally developed, area increasingly gaining in importance (O' Riordan et al., 2001). Public participation is becoming an essential element of the precautionary principle as it grows from simply a tool for dealing with scientific uncertainty, to become part of a movement towards environmental responsibility and sustainability (O' Riordan, 2001; O' Riordan et al., 2001). Openness and honesty are essential to the inclusion of stakeholders such as the public, in environmental decision making. The inclusion of alternative and lay

perspectives, such as traditional indigenous knowledge, is also becoming part of the concept of precaution (Harremöes et al., 2002; Stirling, 2001). Thus the precautionary principle emphasizes that, for PhACs, the concerns of stakeholders, including scientists and lay people, must be considered; and lay concerns about PhACs in the environment must be respected, regardless of whether or not they agree with expert assessments of risk.

The precautionary principle requires that some form of risk mitigation action be considered for PhACs in the environment; however it provides limited guidance in terms of the form this action might take. Government discussion documents on the precautionary principle emphasize the need for management action to be proportional to risk, and to be based on some form of analysis of costs and benefits (Commission of the European Communities, 2000; Government of Canada, 2001, 2003). Doerr-MacEwen and Haight (2005) found that stakeholders for the issue of PhACs in the environment, were concerned that risk management action resulting from the application of precaution be balanced, involve consideration of the distribution of resources to mitigate various risks, and consider the new risks which might be generated by management action. However the precautionary principle itself simply calls for risk management action; as a broad principle, it does not help to define the types of action appropriate under conditions of uncertainty.

3.7. Adaptive planning

As the 'options analysis' stage of risk management is entered, therefore, a new concept is required to help select among policy or management alternatives in conditions of uncertainty: the theory of adaptive planning. The purpose of adaptive planning and management is not to produce stable social, economic, or environmental behavior, but to benefit from change and the unexpected (Briassoulis, 1989; Holling, 1978). Underlying the theory is the concept that, "Attempts to eliminate uncertainty are delusory and often counterproductive." (Holling, 1978, p. 5). Management strategies generated through adaptive planning, therefore, should be resilient, flexible, and capable of being modified in responses to change and surprise (Holling, 1978; Marttunen & Vehanen, 2004). Adaptive planning allows for the creation of plans to manage environmental risks, while

allowing for changing directions as new information about the problem becomes available (Briassoulis, 1989; Marttunen & Vehanen, 2004). Human intervention into environmental processes or structure is experimental (Holling, 1978; Mitchell, 1997), and planners and managers are meant to accept and acknowledge error, and to learn from their mistakes (Briassoulis, 1989). Adaptive planning recognizes the dynamic, complex nature of the environment (Briassoulis, 1989), and gives risk managers a mandate to acknowledge uncertainty, and to act despite uncertainty (Holling, 1978; Lessard, 1998). Public participation is essential at all steps of the adaptive planning process, especially in determining what the desired future environmental conditions are, and how they should be reached (Lessard, 1998). With respect to pharmaceuticals in the environment, adaptive planning favours, at this time, cost-effective, flexible management strategies requiring minimal technological investment. If scientific research increasingly suggests that pharmaceuticals in the environment are harmful to aquatic organisms, ecosystems, or even to human health, more effective but less flexible, more costly management strategies may be required (Fig. 3.5).
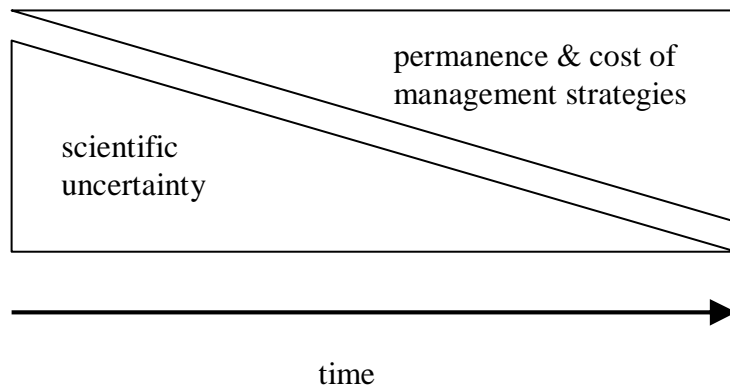
Figure 3.5. *If, with time, scientific evidence increasingly indicates that PhACs in the environment are harmful to aquatic organisms or to human health, more permanent and costly management strategies may be needed. Initially, however, while uncertainty is high, flexible, low cost strategies, meeting the requirements of adaptive planning, should be favored.*

3.8 Application of the precautionary principle and adaptive planning to risk management

By applying the precautionary principle and the theory of adaptive planning to risk management, a modified framework, capable of handling the uncertainty inherent in the issue of PhACs in the environment, is developed (Fig. 3.6). This framework contains a risk assessment stage; however, modified by the application of the precautionary principle, the risk assessment may be qualitative in nature (Commission of the European Communities, 2000), and is based on whatever evidence is available in the scientific literature, through lay knowledge, or can be generated via original research. Of course, management action based on limited information carries the risk of being unsuccessful (Goldstein, 1999). To compensate for this, the theory of adaptive planning is then applied at the options analysis stage. It favors the selection of flexible management strategies, which can be adjusted as understanding of PhACs in the environment evolves (Briassoulis, 1989; Holling, 1978; Lessard, 1998). Furthermore, both the precautionary principle and adaptive planning emphasize the need for stakeholder participation and dialogue, including openness and honesty with the public, in the management of pharmaceuticals in the environment. This framework will provide the basis for discussions of the management of PhACs in the environment throughout this thesis. Chapters 4 to 6 illustrate the application of the precautionary principle and adaptive planning, within the risk management framework developed here, to the management of pharmaceuticals in the environment. The concluding chapter (Ch. 7) discusses the lessons that can be drawn from the practical application of the framework to PhAC management at a local (Ch. 4) and national/international scale (Ch. 5 & 6).

3.9. Conclusions

As the issue of PhACs in the environment is essentially a question of environmental risk, and possibly human health risk, it is reasonable to make use of risk management for the development of strategies to address the issue. However, risk management includes a risk assessment stage which traditionally demands a probabilistic calculation of risk or the construction of an exposure-effect curve (Canadian Standards

Association, 1997; McColl et al., 2000). Scientific understanding of PhACs in the environment is currently insufficient to provide such an assessment of risk; however existing research suggests that PhACs may have sublte, chronic detrimental effects on aquatic organisms (Daughton & Ternes, 1999; Fong, 1998; Purdom et al., 1994). It is unadvisable, therefore, to allow difficulties at the risk assessment stage to stall further
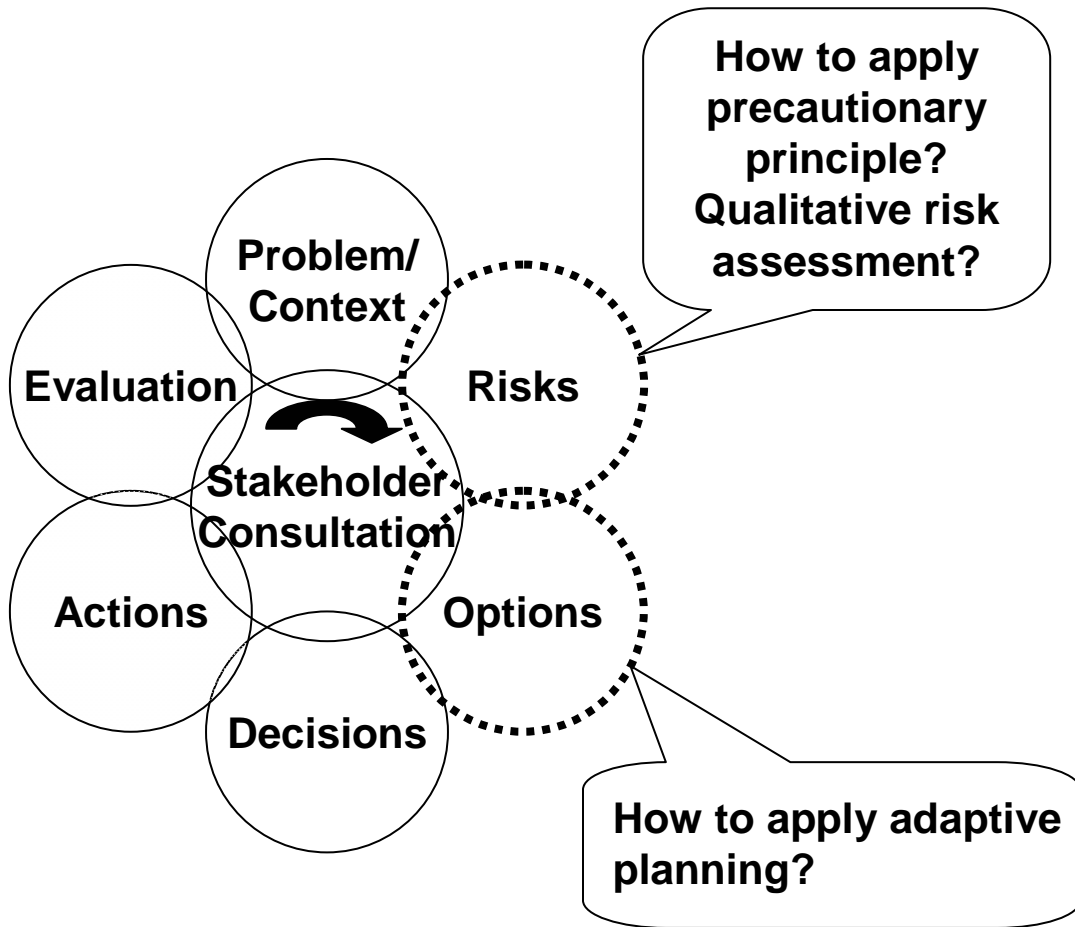
Figure 3.6. Risk management framework (The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997) modified through the application of the precautionary principle and adaptive planning.

considerations of risk management for PhACs. Instead, it is suggested that the precautionary principle be applied to PhACs in the environment. The principle prevents uncertainty from causing delays in management action to mitigate environmental risks; it allows management decisions to be made based on whatever evidence of risk exists, even if causal relationships are not established and exposure-response curves cannot be constructed (Adams, 2002; Commission of the European Communities, 2000; Quijano, 2003). However, engaging in management action when scientific understanding is weak, means that management decisions may be found to be inappropriate or erroneous, and management strategies may need to be changed (Goldstein, 1999). To avoid negative repercussions from change and surprise as the understanding of PhACs in the environment evolves, adaptive planning theory must be applied to the management of pharmaceuticals in the environment. This theory favors the development of flexible management strategies which can be modified as more knowledge regarding PhACs is acquired (Briassoulis, 1989; Holling, 1978; Lessard, 1998). By modifying a traditional risk management framework to include the precautionary principle and adaptive planning, a management process is created which is optimized to account for the uncertainties and complexities inherent in the issue of PhACs in the environment.

3.10. References

Adams, M. (2002). The precautionary principle and the rhetoric behind it. *Journal of Risk Research, 5*(4), 301-316.

Aumonier, J. R. (2003, April 16). *Risk management of pharmaceuticals in the environment: the human pharmaceutical industry viewpoint.* Paper presented at the EnvirPharma, Lyon, France.

Beck, U. (1992). *Risk society: towards a new modernity* (M. Ritter, Trans.). London: Sage Publications.

Briassoulis, H. (1989). Theoretical orientations in environmental planning: an inquiry into alternative approaches. *Environmental Management, 13*(4), 381-392.

Brooymans, H. (2005, Tuesday October 25). Alberta rivers a pharmaceutical soup: Could render antibiotics useless, feminize fish in long run. *The Edmonton Journal,* p. A3.

Cairns, J. J. (1999). Absence of certainty is not synonymous with absence of risk. *Environmental Health Perspectives, 107*(2), A56-A57.

Canadian Standards Association. (1997). *CAN/CSA-Q850-97: Risk management: a guideline for decision-makers.* Etobicoke, ON.

CEPA. (1999). Canadian Environmental Protection Act: The House of Commons of Canada, Bill C-32, as passed by the House of Commons, June 1, 1999.

Commission of the European Communities. (2000). *Communication from the Comission on the precautionary principle* (No. COM (2000)1). Brussels.

Covello, V. T. (1989). Informing people about risks from chemicals, radiation, and other toxic substances: a review of obstacles to public understanding and effective risk communication. In W. Leiss (Ed.), *Prospects and problems in risk communication* (pp. 1-49). Waterloo: University of Waterloo Press.

Daughton, C. G., & Ternes, T. A. (1999). Pharmaceuticals and personal care products in the environment: Agents of subtle change? *Environmental Health Perspectives, 107*, 907-938.

deFur, P. L., & Kaszuba, M. (2002). Implementing the precautionary principle. *The Science of the Total Environment, 288*(155-165).

Doerr-MacEwen, N. A., & Haight, M. E. (2005). Tailoring the precautionary principle to pharmaceuticals in the environment: accounting for experts' concerns. In A. G. Kungolos, C. A. Brebbia & E. Beriatos (Eds.), *Sustainable Development and Planning II* (Vol. 1, pp. 281-291). Southampton: WIT Press.

Dratwa, J. (2002). Taking risks with the precautionary principle: food (and the environment) for thought at the European Commission. *Journal of Environmental Policy and Planning, 4*, 197-213.

Fong, P. P. (1998). Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. *Biology Bulletin, 194*, 143-149.

Goldstein, B. D. (1999). The precautionary principle and scientific research are not antithetical. *Environmental Health Perspectives, 107*(12), A594-A595.

Government of Canada. (2001). *A Canadian perspective on the precautionary approach/principle: discussion document*. Retrieved May 10, 2004, from http://www.ec.gc.ca/econom/discussion_e.htm

Government of Canada. (2003). *A framework for the application of precaution in science-based decision making about risk* (No. ISBN 0-662-67486-3, Cat. no. CP22-70/2003).

Hance, B. J., Chess, C., & Sandman, P. M. (1989). Setting a context for explaining risk. *Risk Analysis, 9*(1), 113-117.

Harremöes, P., Gee, D., MacGarvin, M., Stirling, A., Keys, J., Wynne, B., et al. (2002). Twelve late lessons. In P. Harremöes, D. Gee, M. MacGarvin, A. Stirling, J. Keys, B. Wynne & S. Guedes Vaz (Eds.), *The precautionary principle in the 20th century*. London: Earthscan Publications Ltd.

Healey, S. (2001). Risk as social process: the end of 'the age of appealing to the facts'? *Journal of Hazardous Materials, 86*, 39-53.

Health Canada. (1998, December 31 2002). *The HPB risk management framework*. Retrieved February 4, 2004, from http://www.hc-sc.gc.ca/sab-ccs/mar1998_apph_hpb_risk_e.html

Henschel, K.-P., Wenzel, A., Diedrich, M., & Fliedner, A. (1997). Environmental hazard assessment of pharmaceuticals. *Regulatory Toxicology and Pharmacology, 25*, 220-225.

Holling, C. S. (Ed.). (1978). *Adaptive environmental assessment and management*. Chichester: John Wiley & Sons.

Hood, C., Jones, D. K. C., Pidgeon, N., Turner, B., Gibson, R., Bevan-Davies, C., et al. (1992). Risk management. In The Royal Society (Ed.), *Risk: analysis, perception and management* (pp. 135-200). London: The Royal Society.

Hrudey, S. E. (1996). A critical review of current issues in risk assessment and risk management. In D. Del Bel Belluz & J. H. Shortreed (Eds.), *Technical risk issues in business and regulatory decision-making* (pp. 17-31). Waterloo: Institute for Risk Research.

Jardine, C. G., & Hrudey, S. E. (1997). Mixed messages in risk communication. *Risk Analysis, 17*(4), 489-498.

Jobling, S., Nolan, M., Tyler, C. R., Brightly, G., & Sumpter, J. P. (1998). Widespread sexual disruption in wild fish. *Environmental Science and Technology, 32*, 2498-2506.

Jordan, A., & O' Riordan, T. (1999). The precautionary principle in contemporary environmental policy and politics. In C. Raffensperger & J. A. Tickner (Eds.), *Protecting public health & the environment: implementing the precautionary principle* (pp. 15-35). Washington, D.C.: Island Press.

Kriebel, D., Tickner, J., Epstein, P., Lemons, J., Levins, R., Loechler, E. L., et al. (2001). The precautionary principle in environmental science. *Environmental Health Perspectives, 109*(9), 871-876.

Länge, R., & Dietrich, D. (2002). Environmental risk assessment of pharmaceutical drug substances -- conceptual considerations. *Toxicology Letters, 131*, 97-104.

Leiss, W., & Chociolko, C. (1994). *Risk and responsibility*. Montreal & Kingston: McGill-Queen's University Press.

Lessard, G. (1998). An adaptive approach to planning and decision-making. *Landscape and Urban Planning, 40*, 81-87.

Marttunen, M., & Vehanen, T. (2004). Toward adaptive management: the impacts of different management strategies on fish stocks and fisheries in a large regulated lake. *Environmental Management, 33*(6), 840-854.

McColl, S., Hicks, J., Craig, L., & Shortreed, J. H. (2000). *Environmental health risk management: a primer for Canadians*. Waterloo: Network for Environmental Risk Assessment and Management.

McGarvin, M. (2001). Science, precaution, facts and values. In T. O' Riordan, J. Cameron & A. Jordan (Eds.), *Reinterpreting the precautionary principle* (pp. 35-60). London: Cameron May.

Mitchell, B. (1997). *Resource and environmental management*. Harlow, UK: Pearson Education.

Mittelstaedt, M. (2003). Drug traces found in cities' water. *The Globe and Mail, February 10,* p. 1.

National Research Council. (1983). *Risk assessment in the federal government: managing the process*. Washington, D.C.: National Academy Press.

O' Riordan, T. (2001). The precautionary principle and civic science. In T. O' Riordan, J. Cameron & A. Jordan (Eds.), *Reinterpreting the precautionary principle* (pp. 95-111). London: Cameron May.

O' Riordan, T., Jordan, A., & Cameron, J. (2001). The evolution of the precautionary principle. In T. O' Riordan, J. Cameron & A. Jordan (Eds.), *Reinterpreting the precautionary principle* (pp. 9-33). London: Cameron May.

Purdom, C. E., Hardiman, P. A., Bye, V. J., Eno, N. C., Tyler, C. R., & Sumpter, J. R. (1994). Estrogenic effects of effluents from sewage treatment works. *Chemical Ecology, 8*, 275-285.

Quijano, R. F. (2003). Elements of the precautionary principle. In J. A. Tickner (Ed.), *Precaution, environmental science, and preventive public policy* (pp. 21-27). Washington: Island Press.

Renn, O. (2004). Perception of risks. *Toxicology Letters, 149*, 405-413.

Rogers, M. D. (2001). Scientific and technological uncertainty, the precautionary principle, scenarios and risk management. *Journal of Risk Research, 4*(1), 1-15.

Rogers, M. D. (2003). Risk analysis under uncertainty, the Precautionary Principle, and the new EU chemicals strategy. *Regulatory Toxicology and Pharmacology, 37*, 370-381.

Ruckelhaus, W. D. (1990). Risk, science and democracy. In T. S. Glickman & M. Gough (Eds.), *Readings in risk* (pp. 105-118). Washington: Resources for the future.

Sanderson, H., Johnson, D. J., Reitsma, T., Brain, R. A., Wilson, C. J., & Solomon, K. R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology, 39*, 158-183.

Santillo, D., Stringer, R. L., Johnston, P. A., & Tickner, J. (1998). The precautionary principle: protecting against failures of scientific method and risk assessment. *Marine Pollution Bulletin, 36*(12), 939-950.

Slovic, P. (1987). Perception of risk. *Science, 236*, 280-285.

Slovic, P. (1993). Perceived risk, trust, and democracy. *Risk Analysis, 13*(6), 675-682.

Slovic, P. (2001). The risk game. *Journal of Hazardous Materials, 86*, 17-24.

Somers, E. (1995). Perspectives on risk management. *Risk Analysis, 15*(6), 677-683.

Stirling, A. (2001). The precautionary principle in science and technology. In T. O' Riordan, J. Cameron & A. Jordan (Eds.), *Reinterpreting the precautionary principle* (pp. 35-60). London: Cameron May.

The Presidential/Congressional Commission on Risk Assessment and Risk Management. (1997). *Framework for environmental health risk management: final report, volume 1*. Retrieved June 2, 2004, from http://www.riskworld.com/Nreports/1997/risk-rpt/pdf/EPAJAN.PDF

Turner, B. (1994). The future for risk research. *Journal of Contingencies and Crisis Management, 2*(3), 146-156.

United Nations General Assembly. (1992). *Report of the United Nations conference on environment and development* (No. A/CONF.151/26 Vol. I). Rio de Janeiro.

Weterings, R. A. P. M., & Van Eijndhoven, J. C. M. (1989). Informing the public about uncertain risks. *Risk Analysis, 9*(4), 473-482.

Wingspread Conference on the Precautionary Principle. (1998). *Wingspread Statement*. Retrieved October 24, 2003, from http://www.sehn.org/wing.html

Chapter 4: Case study on the management of human PhACs in the environment (Region of Waterloo, ON)

4.1 Introduction

The management of human pharmaceuticals (or PhACs, pharmaceutically active compounds) in aquatic environments can be conducted at several scales, from local to international. Large-scale approaches, such as those at international, national, and provincial levels, are important in terms of developing regulations and providing funding. However, high concentrations of pharmaceuticals in the environment are often localized. Human pharmaceuticals are usually found at their highest concentrations in densely populated urban areas, especially downstream from municipal wastewater treatment plants (Carballa et al., 2004; Heberer, Schmidt-Bäumier, & Stan, 1998; Stumpf, Ternes, Wilken, Rodrigues, & Baumann, 1999; Ternes, 1998). Municipalities can, therefore, make important contributions in mitigating environmental contamination by pharmaceuticals.

The Regional Municipality of Waterloo (Ontario, Canada), located in the Grand River Watershed (Fig. 4.1), provides a good location for a case study to examine possible local management strategies for PhACs in the environment. It is a mid-sized municipality of approximately 450 000 residents, comprised of the lower-tier municipalities of Waterloo, Kitchener, and Cambridge, as well as several smaller townships (Region of Waterloo, 2005). The Region of Waterloo is known for its efforts to protect the local environment; it has won awards for its forward-looking environmental planning and management, including its water protection programs (Canadian Centre for Pollution Prevention, 2005; Region of Waterloo, 2002). The Region therefore is likely to be interested in addressing the issue of PhACs in local surface water and groundwater in the future.

Management of environmental risks requires both a scientific evaluation of risk, and consideration of the values and concerns of stakeholders, as discussed in Chapter 3. However, the effects of PhACs on aquatic organisms and ecosystems at environmental concentrations are poorly understood and current risk assessment methodology is inadequate for the detection of the suspected subtle, chronic effects of pharmaceuticals

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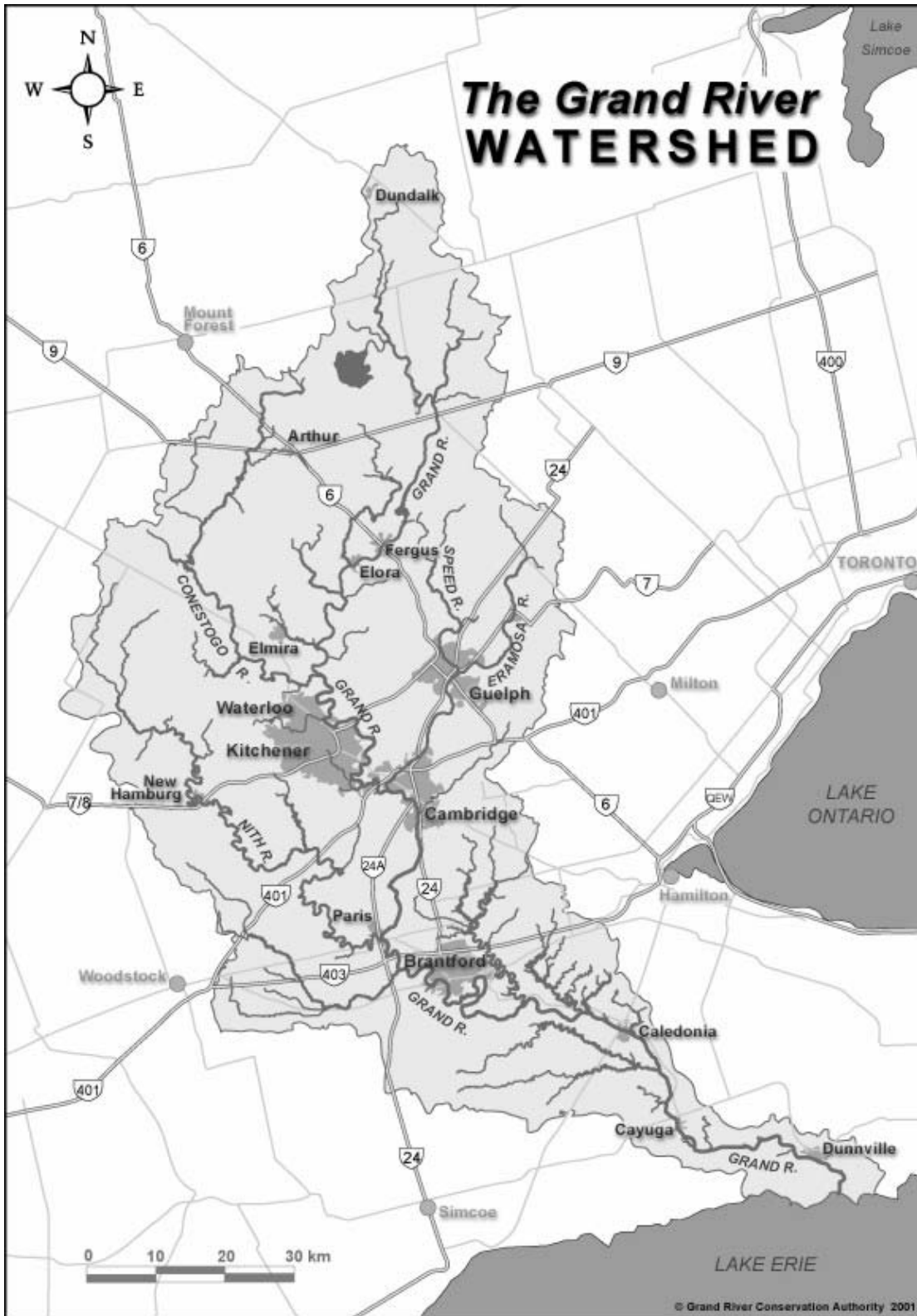
Figure 4.1. Map of the Grand River Watershed (Grand River Conservation Authority, 2001)

(Bound & Voulvoulis, 2004; O'Brien & Dietrich, 2004; Sanderson et al., 2004; Seiler, 2002) (Ch. 2). Predicted no effects concentration (PNEC) data are available for some of the most commonly detected pharmaceuticals, but they are based on acute toxicity tests, which are not appropriate for the detection of the subtle effects of pharmaceuticals (Länge & Dietrich, 2002; Sanderson et al., 2004; Sanderson, Johnson, Wilson, Brain, & Solomon, 2003). Even when chronic toxicity tests have been performed, difficulties in the selection of appropriate test species, endpoints, and the complexities of mixture effects, among other factors, make the relevance of the PNEC values questionable. As a result, calculations of risk quotient, PEC/PNEC (PEC: predicted environmental concentrations) must be interpreted with care. The main purpose of this chapter is therefore not to determine whether environmental concentrations of pharmaceuticals in the Waterloo Region exceed a critical value, as such a value cannot be accurately determined at this time. Instead, based on four premises, it is assumed that some municipalities, in Canada and other countries, may consider taking management action to reduce the release of pharmaceuticals to the environment in the near future. The premises are: 1) The scientific literature contains examples where PhACs have had effects on the development, reproduction, and behaviour, of aquatic organisms, among other effects, at low concentrations. Effects have been found in both field (Jobling, Nolan, Tyler, Brightly, & Sumpter, 1998; Larsson et al., 1999) and laboratory (Brooks et al., 2003; Pascoe, Karntanut, & Müller, 2003; Wilson, Smith, Denoyelles, & Larive, 2003) studies; for example, the feminization of fish exposed to 17α-ethinylestradiol (EE2) (Jobling et al., 1998; Purdom et al., 1994), and the spawning of mussels exposed to fluoxetine (Brooks et al., 2003; Fong, 1998, 2001); as well as effects of the antibiotic ciprofloxacin on algal community structure and function (Wilson et al., 2003) have been observed. 2) The precautionary principle suggests that when there are grounds for concern about the environmental impact of a substance, reasonable and proportional management action should be taken to mitigate the environmental impacts (Commission of the European Communities, 2000; Government of Canada, 2001; United Nations General Assembly, 1992). The precautionary principle is embodied in the Canadian Environmental Protection Act (CEPA, 1999) and is considered by many to be a principle of international law (Cameron, 2001) 3) Adaptive planning/management theory suggests that risk

management in the face of uncertainty is possible and indeed desirable. Uncertainty can be accommodated by adjusting management strategies as understanding of the environmental impacts of PhACs evolves. (Briassoulis, 1989; Holling, 1978; Lessard, 1998); and 4) stakeholders, especially the public, may want management action taken to reduce the release of PhACs to aquatic environments.

This chapter consists of two components; a natural scientific component (a technical assessment of water chemistry) and a social scientific component (an assessment of local values and concerns). The purposes of the *scientific* component of this study are threefold: 1) To determine whether detectable concentrations of human pharmaceuticals are being released from wastewater treatment plants (WWTPs) to aquatic environments in the Waterloo Region; 2) to determine whether or not the loading of PhACs to the environment from wastewater treatment plants (WWTPs) in Waterloo is comparable to those of other urban areas. If PhAC loading is similar to or higher than in other municipalities, Waterloo may be a good candidate for management action; if PhAC concentrations are much lower than in other urban areas, the Region of Waterloo may prefer to focus on other environmental concerns. 3) to determine which pharmaceuticals are being released at the highest concentrations, or at high concentrations in comparison with other municipalities, as this knowledge may be of aid in the development of management strategies.

The second component of this study involves assessment of the values and concerns of local citizens. Public consultation is an essential component of all planning decisions, playing a key role in planning theory (Arnstein, 1969; Friedmann, 1987; Lessard, 1998) and practice (Beierle & Konisky, 2001; McDaniels, Gregory, & Fields, 1999). The public represent a key stakeholder group whose consultation is an important and necessary component of risk management (Canadian Standards Association, 1997; Dyck, Del Bel Belluz, & Craig, 1999; Petts, 1994). Other stakeholders such as the pharmaceutical industry are better included at a broader scale; Ch. 5 discusses consultation with members of the pharmaceutical industry and other stakeholders. This part of this study will assess the values, attitudes, desires and behaviours of residents of the Region of Waterloo, regarding human pharmaceuticals in the environment. This initial form of assessment of public values is required as a basis for future public

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consultation if the Region of Waterloo decides to further explore management action for PhACs in the environment.

4.2 Location selection

To assess possible management strategies for PhACs in the environment in which the Region of Waterloo might engage, two communities within the region were chosen to conduct the natural scientific and social scientific components of the study: The municipality of Kitchener and the retirement community of Foxboro Green, located on the Western side of the Region (Fig. 4.2). Kitchener has a mid-sized urban population served by a municipal wastewater treatment plant and is the largest municipality within the Region of Waterloo. It provides a good basis to assess and make recommendations regarding management of PhACs in the Region. Such information is required to make comparison with municipalities elsewhere in the world. Foxboro was chosen because it
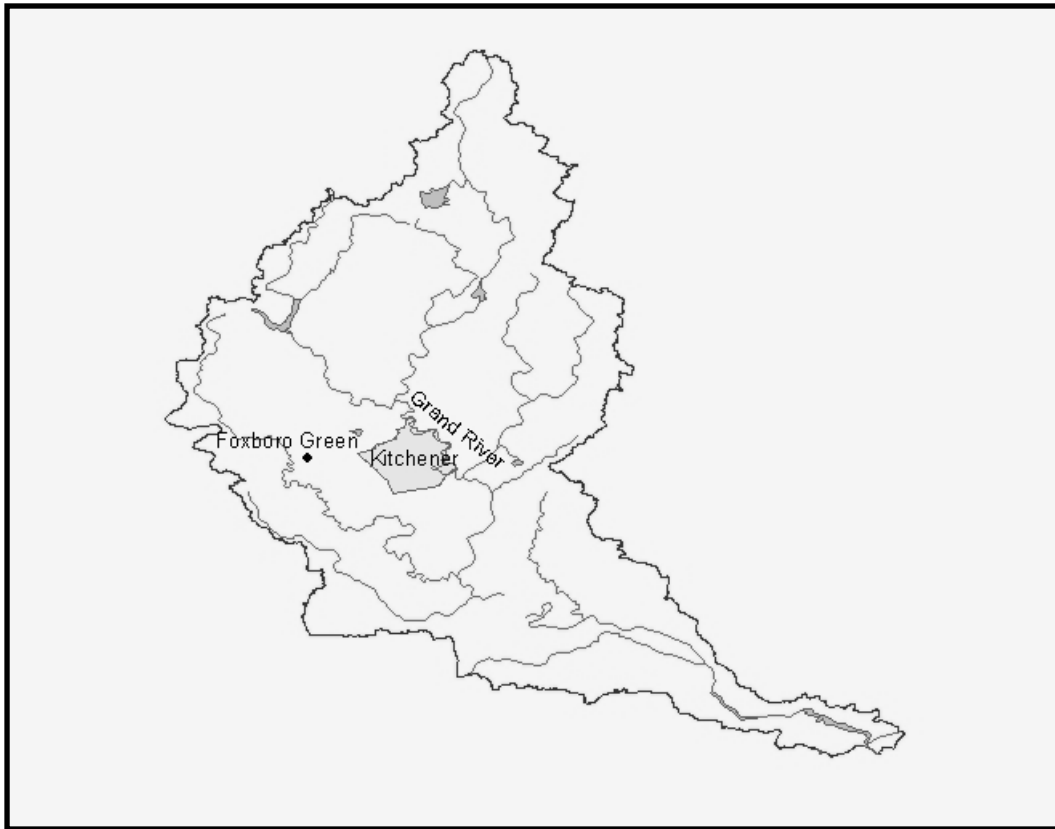
Figure 4.2. Map showing Grand River watershed, Grand River, Kitchener and Foxboro Green.

is a retirement community. Its residents – seniors -- are expected to use a greater number of pharmaceuticals that other age groups, and are therefore likely to contribute highly to the release of PhACs to the environment. Furthermore, the community has its own wastewater treatment plant, to which the residents are the only contributors of PhACs. Water chemistry data from Kitchener and Foxboro are combined with value assessment in this local study of PhAC management opportunities.

4.3 Methods
4.3.1 Analysis of PhACs in wastewater
4.3.1.1 Sample collection

Samples of wastewater influent and effluent were collected from the Foxboro and Kitchener WWTPs using an autosampler. For each site and effluent type, 3 L of wastewater were collected in the form of composite samples over a 24-hour period. The 3 L samples were then split into 3 1L sample bottles, for the analysis of acidic pharmaceuticals, neutral pharmaceuticals and antibiotics. A water blank, trip blank and travel blank were also collected. Samples were collected in amber glass bottles, pre-cleaned with solvent, acid, and deionized water and baked. In addition, samples were collected and analyzed for water quality parameters related to the working of the plant (Table 4.1).

Twenty-four hour composite sampling, with sub-sample collection every 30 minutes, was conducted for both influent and effluent at the Kitchener and Foxboro WWTPs. At the Foxboro WWTP, influent sampling began at 9:40 am on Tuesday July 27th, 2004, and effluent sampling began at 12:40 on the same day, to account for the 3 hour retention time at the plant (Ministry of the Environment, 2001). The sampling period for the Kitchener WWTP influent began at 15:00 Wednesday, July 28th, 2004, and sampling of the effluent began at 7:00 am on Thursday July 29th, to account for the 16 hour retention time at the plant (Region of Waterloo, 2003). Samples were kept cool (8-12^0C). After collection, samples were refrigerated at ~4^oC, in the dark, and shipped to Trent University for analysis on Thursday, July 29th. Ideally, samples would have been collected over several days and in several different seasons, to ensure reproduceability

and representativeness of data. Due to a lack of funding, this was not possible; therefore care should be taken in interpreting data, as it may not be representative of pharmaceutical loading from the plants on other days and at other times of year.

4.3.1.2 Analysis of PhACs

Analyses of PhACs in wastewater samples were conducted by C. Metcalfe and X. Zhao, at Trent University.   Volumes of 25 mL of raw wastewater or 50 mL of final wastewater were extracted by solid phase extraction (SPE) for the analysis of sulfonamide and fluoroquinolone antibiotics and acidic and neutral drugs, according to the methods described by Miao, Bishay, Chen & Metcalfe, (2004) and Metcalfe, Miao, Koenig and Struger (2003). Extracts were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS), using electrospray ionization (ESI) for the fluoroquinolone antibiotics and acidic drugs and atmospheric pressure chemical ionization (APCI) for the neutral drugs and sulfonamide antibiotics. The LC-MS/MS system was an Agilent 1100 series binary pump with autosampler and QTrap mass spectrometer (MDS SCIEX, Toronto) equipped with either the ESI or APCI source, and operated by Analyst 1.4 software. The chromatography was conducted with Genesis C18 columns of 150×3 mm or 150×2.1 mm, depending on the ion source utilized. Specific instrumental conditions for the analyses of the various classes of pharmaceuticals can be found in Appendix A; detection limits for the analytes and results of analyses of blanks are listed in Appendix B.

4.3.2. Social surveys

Surveys were conducted in Kitchener and in Foxboro to assess the attitudes, values and behaviors of the public, related to pharmaceuticals in the environment. The surveys were comprised of mainly close-ended questionnaires (Appendix C). Convenience surveys were used, with respondents being recruited in person (i.e. respondents were stopped on the sidewalk and asked to participate; they were not sampled randomly). Recruitment in Foxboro and Kitchener occurred at a recreation complex and in a mini-mall, respectively. A total of 128 respondents were surveyed, comprised of 44 respondents from Foxboro and 84 respondents from Kitchener.

Respondents were given the option of completing the survey with the help of the survey administrator, or completing the surveys on their own. The majority of respondents chose to complete the surveys with the help of the administrator.

Parameter	Kitchener Influent	Kitchener Effluent	Foxboro Influent	Foxboro Effluent
Ammonia-N	5.34	18.8	22.4	20.6
BOD -- Biochemical Oxygen Demand (5-day)	209	10.9	237	24.0
Nitrate-N	<0.10	0.85	<0.10	<0.10
Nitrite-N	<0.050	0.428	<0.050	<0.050
TKN -- Total Kjeldahl Nitrogen	30.7	21.9	49.7	22.9
TSS -- Total Suspended Solids	210	8.8	414	30.5
Phosphorous	5.11	0.748	10.8	3.88
pH (Composite)	8.28	7.89	7.76	7.69

Table 4.1. Parameters related to WWTP plant functioning, from samples collected at the Kitchener and Foxboro WWTPs July 28, 2004. Note: MOE guidelines for effluent are: total phosphorous, 1.0 mg/L; BOD 25 mg/L; total suspended solids 25 mg/L.

4.4. Wastewater treatment plant parameters

4.4.1 Kitchener wastewater treatment plant

The Kitchener wastewater treatment plant is located on the south bank of the Grand River, to which effluent is discharged. It treats wastewater for a population of 180 000 residents, in addition to businesses and industries. No effluent from pharmaceutical manufacturers is treated by this plant. It receives an average flow of approximately 60 000 m^3/d, but is designed for a maximum capacity of 122 740 m^3/d (Region of Waterloo, 2003). The plant employs a conventional activated sludge process to treat wastewater. The primary treatment component involves screening removal, grit removal, and primary clarification; the secondary treatment component includes mechanical aeration and mixing, secondary clarification with activated sludge return and

wasting, anaerobic sludge digestion in a two stage process, chlorine disinfection, phosphorus removal and sludge transfer (See Appendix D for photos) (Region of Waterloo, 2003). Total retention time is between 13-19 hours, with a hydraulic retention time of 4-7 hours during the aeration stage. The plant is operating within the Ministry of Environment Guidelines (Table 4.1) for parameters including biochemical oxygen demand (BOD), total phosphorus and total suspended solids. Sludge from the treatment process is used as a fertilizer and soil conditioner for agricultural lands throughout the region (Region of Waterloo, 2003).

4.4.2 Foxboro Green wastewater treatment plant

The wastewater treatment plant for the Foxboro retirement community has a capacity of 78 m^3/d and serves 65 residences. The wastewater treatment plant is comprised of a primary settling tank with a retention time of 2 hours; two rotating biological contactors with a total surface area of 3000 m^2; a denitrification chamber of 1887 m^2, using molassess as a carbon source and a final clarifier of 4.8 m^3 with a final sludge collection zone (See Appendix D for photos). Treated wastewater is released through a subsurface sewage disposal system comprised of 3 conventional absorption trench leaching beds (Ministry of the Environment, 2001). The Foxboro WWTP has a lower treatment efficiency than the Kitchener WWTP (Table 4.1).

4.5 Discussion of results

4.5.1 PhACs in wastewater

Twenty-one of the 26 PhACs analyzed in the wastewater treatment samples from both plants were detected at ng/L and μg/L concentrations (Table 4.2). The residuals of acid and neutral drugs in the Kitchener influent were in the same range as those reported in the literature internationally (Table 4.3; Fig. 4.3) and were similar to those found by Lee, Sarafin, Peart & Svoboda (2004) in for a wastewater treatment plant in Guelph, Ontario, a city of comparable population. Concentrations were generally lower than those found by Metcalfe et al. (2003) for a range of Canadian WWTP influents. Concentrations of acidic and neutral drugs in the WWTP effluents from both

Compound	Kitchener Effluent (µg/L)	Kitchener Influent (µg/L)	Foxboro Effluent (µg/L)	Foxboro Influent (µg/L)
Neutral Drugs				
Caffeine	1.25	7.20	1.56	24.40
Carbamazepine	0.666	0.321	0.024	0.090
Cotinine	0.122	2.028	0.188	0.292
Cyclophosphamide	0.006	0.018	<0.003	<0.001
Fluoxetine	0.02	0.02	<0.01	<0.005
Pentoxifylline	0.03	0.007	<0.002	<0.001
Trimethoprim	1.968	12.000	0.109	0.012
Acidic Drugs				
Bezafibrate	0.164	0.407	1.823	NA
Clofibric Acid	<0.007	<0.007	<0.007	NA
Diclofenac	0.12	0.29	0.19	NA
Fenoprofen	<0.02	<0.008	<0.02	NA
Gemfibrozil	0.086	0.169	2.111	NA
Ibuprofen	0.28	4.47	2.99	NA
Indomethacin	0.3	0.1	0.9	NA
Ketoprofen	<0.008	<0.008	<0.008	NA
Naproxen	0.96	1.76	2.22	NA
Sulfonamides				
Sulfacetamide	<0.02	<0.02	<0.02	<0.02
Sulfapyridine	0.02	0.21	0.12	<0.005
Sulfadiazine	<0.002	<0.004	<0.002	<0.004
Sulfamethoxazole	3.05	21.291	0.677	0.041
Sulfisoxazole	<0.001	<0.001	0.001	0.023
Sulfamethazine	<0.002	<0.003	0.002	0.018
Fluoroquinolones				
Ciprofloxacin	0.11	0.99	1.41	0.53
Norfloxacin	0.01	0.47	0.50	0.22
Ofloxacin	0.47	0.49	0.22	0.16

Table 4.2. Concentrations of pharmaceutical analytes in wastewater. N.A: not available due to analytical difficulties. Note: standard deviations, detection limits, and analyses of blanks can be found in Appendix B.

Influent (µg/L)	This study: Kitchener	Canada: Guelph, Lee et al. (2004)[1]	Canada, Metcalfe et al. (2003)[2]	Brazil: Rio de Janeiro Stumpf et al. (1999)[3]	Germany : Berlin, Heberer (2002b)[4]	Germany : BLAC (2003)[2]
Bezafibrate	0.407		0.6	~1.18		~3.0
Caffeine	7.20				230	
Carbamazepine	0.321		0.7		1.78	~1.7
Clofibric Acid	<0.007		ND	~1.0	0.46	~0.3
Cyclophosphamide	0.018		ND			
Diclofenac	0.29	0.07	1.3	~0.78	3.02	~1.8
Fenoprofen	<0.008		1.8			
Gemfibrozil	0.169	0.14	0.7	~0.35		
Ibuprofen	4.47	6.22	38.7	~0.33		~3.1
Indomethacin	0.1	0.19		~0.92	0.8	ND
Ketoprofen	<0.008	0.07	5.7	~0.58	0.3	~0.2
Naproxen	1.76	2.31	40.7	~0.60	0.44	~0.4
Pentoxifylline	0.007		ND			
Effluent (µg/L)	This study: Kitchener	This study: Foxboro	Canada: Guelph, Lee et al. (2004)[1]	Canada, Metcalfe et al. (2003)[2]	Brazil: Rio de Janeiro Stumpf et al. (1999)[3]	Germany: Berlin, Ternes (1998)[2]
Bezafibrate	0.164	1.823		0.2	~0.57	2.2
Caffeine	1.25	1.56				
Carbamazepine	0.666	0.024		0.7		2.1
Clofibric Acid	<0.007	<0.007		ND	~0.66	0.36
Cyclo-phosphamide	0.006	<0.003		ND		ND
Diclofenac	0.12	0.19	0.08	ND	~0.19	0.81
Fenoprofen	<0.02	<0.02		ND		ND
Gemfibrozil	0.086	2.111	0.08	1.3	~0.17	0.40
Ibuprofen	0.28	2.99	0.11	4.0	~0.08	0.37
Indomethacin	0.3	0.9			~0.17	0.27
Ketoprofen	<0.008	<0.008	0.07	ND	~0.17	0.20
Naproxen	0.96	2.22	0.36	12.5	~0.15	0.30
Pentoxifylline	0.03	<0.002		0.5		

[1] Mean calculated from duplicate samples

[2] Median based on sampling of multiple WWTPs

[3] Interpreted from graph; for single WWTP

[4] Averages from multiple WWTPs, compiled from various sources

[5] Median from multiple WWTPs, interpreted from graph

Table 4.3. Concentrations of acidic and neutral PhACs in WWTP influent and effluent in this and other studies (ND=not detected).
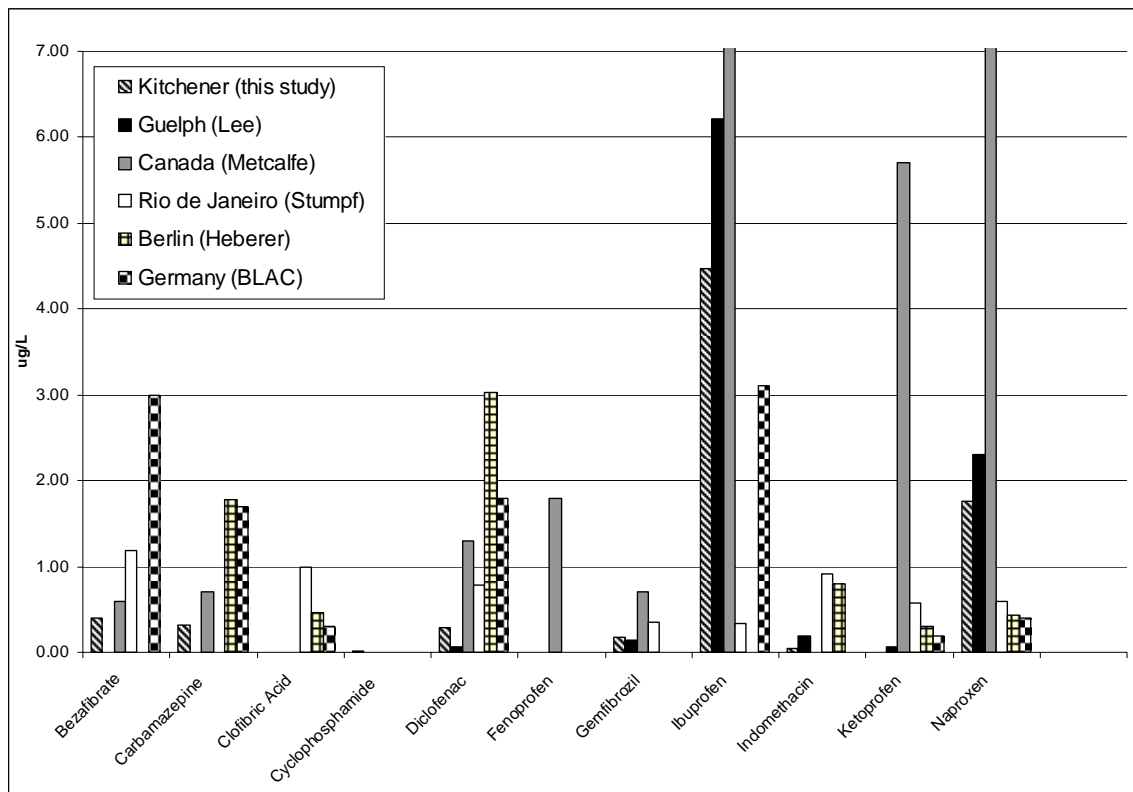
Figure 4.3. Concentrations of acidic and neutral PhACs in wastewater treatment plant influent, in this study and others internationally. Note: Not all studies measured concentrations of each PhAC.

Kitchener and Foxboro were also within the range of concentrations found internationally (Table 4.3; Fig. 4.4). PhAC concentrations for Foxboro were higher than Kitchener but were similar to those previously reported for WWTPs in the Great Lakes Region (Metcalfe, Koenig et al., 2003) and in Berlin (Ternes, 1998).

The results were somewhat different for antibiotics. The concentrations of antibiotics in the effluent from the Kitchener and Foxboro plants were generally higher than those found in other Canadian and international studies (Table 4.4, Fig. 4.5). In particular, the concentration of sulfamethoxazole in the Kitchener effluent was at least three times greater than the concentration measured in the effluents of other WWTPs. Concentrations of the fluoroquinolone antibiotics were especially high in the Foxboro effluent, with ciprofloxacin and norfloxacin concentrations being an order of magnitude higher than those found in other WWTP effluents. The high concentration of
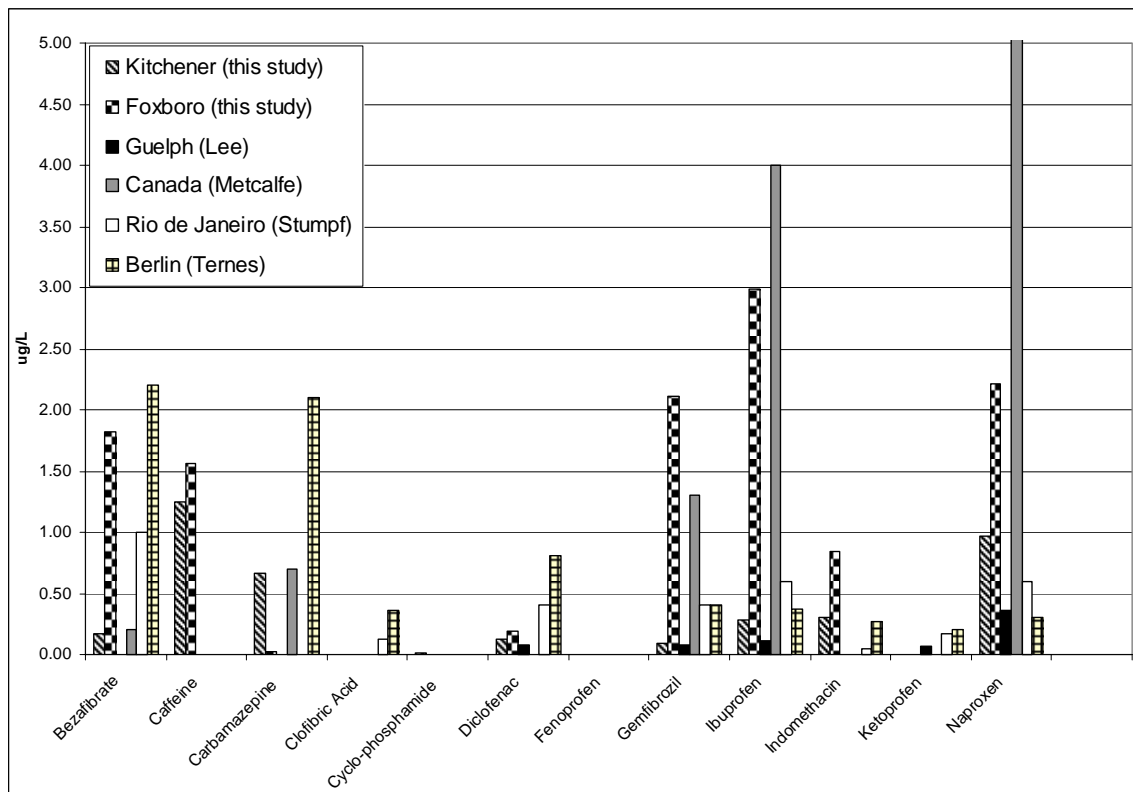
Figure 4.4. Concentrations of acidic and neutral PhACs in wastewater treatment plant effluent, in this study and others internationally. Note: Not all studies measured concentrations of each PhAC.

Effluent (μg/L)	Kitchener: this study	Foxboro: this study	Canada: Miao et al.(2004)[1]	Germany: Hirsch et al. (1999)[1]	Switzerland: Zurich, Golet et al. (2003)[2]
Ciprofloxacin	0.11	1.41	0.118		0.071
Norfloxacin	0.01	0.50	0.050		0.051
Ofloxacin	0.47	0.22	0.094		
Sulfacetamide	<0.02	<0.02	0.064		
Sulfadiazine	<0.002	<0.002	0.019		
Sulfamethazine	<0.002	0.002	0.363	ND	
Sulfamethoxazole	3.05	0.677	0.243	0.40	
Sulfapyridine	0.02	0.12	0.081		
Sulfisoxazole	<0.001	0.001	0.019		

[1] Median based on sampling of multiple WWTPs
[2] Average of multi-day sampling from one tertiary WWTP

Table 4.4. Concentrations of antibiotics in wastewater treatment plant effluents in this study and others internationally (ND=not detected).
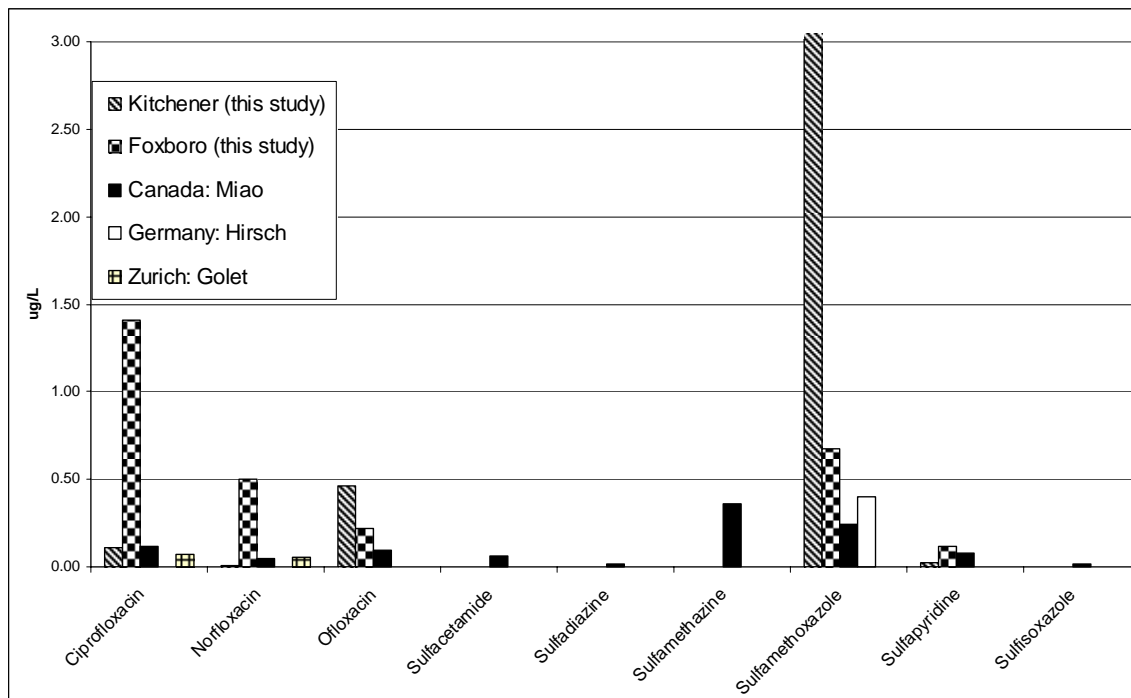
Figure 4.5. Concentrations of antibiotics in wastewater treatment plant effluent in this study and others internationally. Note: Not all studies measured concentrations of each antibiotic.

sulfamethoxazole in the Kitchener effluent is somewhat surprising. However, given the limited sampling conducted, it is possible that the concentration is an outlier, due to an unusual loading of sulfamethoxazole on the day of sampling. The high concentrations of acidic and neutral drugs, and sulfamethoxazole, in the Foxboro effluent, are less surprising, however, for two reasons: 1) the elderly population of the Foxboro retirement community likely consumes greater quantities of medications than 'average' urban populations. 2) the Foxboro plant is operating sub-optimally (Section 4.4.2, Table 4.1) and other studies have found that WWTPs which operate sub-optimally with regard to normal parameters such as BOD, usually do not successfully remove PhACs (Clara, Kreuzinger, Strenn, Gans, & Kroiss, 2005; Vieno, Tuhkanen, & Kronberg, 2005). The elevated concentrations of antibiotics in Waterloo Region effluents are somewhat concerning, as antibiotics in wastewater and the environment may contribute to resistance among microbes (Goñi-Urriza et al., 2000; Guardabassi, Petersen, Olsen, & Dalsgaard, 1998; Jorgensen & Halling-Sorensen, 2000; Kümmerer & Henninger, 2003).

Furthermore, concerns have been raised about the ecotoxicity of some of the antibiotics measured, particularly ciprofloxacin (Hartmann, Alder, Koller, & Widmer, 1998; Kümmerer, Al-Ahmad, & Mersch-Sundermann, 2000; Wilson et al., 2003). In a large-scale German study, ciprofloxacin was one of only two substances which had a predicted environmental concentration (PEC) exceeding its predicted no-effects concentration (PNEC) (Bund/Länderausschuss für Chemikaliensicherheit (BLAC), 2003). The report suggests that ciprofloxacin should be classified as potentially harmful to the environment. Table 4.5 illustrates the risk quotients for several pharmaceuticals in the Grand River, determined from the effluent concentrations from the Kitchener WWTP, a dilution factor of 10, and the PNEC values of the German report.

PhAC	PEC in Grand River (µg/L)	PNEC (µg/L)	Risk Quotient (PEC/PNEC)
Carbamazepine	0.03	2.5	0.01
Ciprofloxacin	0.1	0.018	6
Diclofenac	0.03	100	0.0003
Ibuprofen	0.4	7.1	0.06

Table 4.5. Risk Quotients calculated for selected pharmaceuticals in the Grand River. PECs (Predicted Environmental Concentrations) are based on a 10-fold dilution factor between concentrations in the Kitchener WWTP effluent and the river. A 10-fold dilution factor between WWTP and surface water is typical for calculations of PEC for environmental risk assessments for pharmaceuticals (CPMP, 2001; Golet, Alder, & Giger, 2002). However, using a factor of 10 does not allow for highly accurate predictions of environmental concentrations, as it does not account for the size of the mixing zone or the flow conditions and dilution of a specific river. For the Grand River in low flow, dilution at the point of entry of wastewater into the river is approximately 3-fold (calculated based on data from the Grand River Conservation Agency, 2007). PNECs (Predicted No Effects Concentrations) are taken from a study by the German Government (Bund/Länderausschuss für Chemikaliensicherheit (BLAC), 2003).

The risk quotient for ciprofloxacin in the Grand River is greater than 1 because of its toxicity to bacteria. This raises concerns about the potential impact of ciprofloxacin on aquatic species in the Grand River. While PhACs in the Foxboro effluent are not likely to impact local groundwater, due to the presence of an extensive aquitard (pers. comm., D. Andrews, manager of wastewater operations, Region of Waterloo, 2005), Foxboro residents could nevertheless be concerned about the release of antibiotics such as ciprofloxacin to the subsurface, particularly given recent media attention to the issue of PhACs in the environment. (Brooymans, 2005; Mittelstaedt, 2003; Stevenson, 2003). Reducing the concentrations of antibiotics in local WWTP effluents can therefore be considered a worthwhile goal of potential management action in the Waterloo Region. This is necessary for both scientific or risk-related reasons but also to improve public perception of water quality.

Most studies of PhACs in the environment are based on measurements of concentrations, but it is also of interest to calculate the loading of pharmaceuticals to the environment. The loading of PhACs entering and leaving the Kitchener and Foxboro wastewater treatment plants is shown in Table 4.6. Loading rates were calculated based on the average daily volume of wastewater treated by each plant; 60 000 m^3/d and 78 m^3/d in Kitchener and Foxboro, respectively (See Section 4.4). The environmental loading of PhACs from the Kitchener plant is several orders of magnitude higher than from the Foxboro plant because it treats a much larger volume of wastewater on a daily basis.

Also of interest is the loading of PhACs per person; or the contribution of each resident to the environmental loading of PhACs. PhAC loading rates were calculated for Kitchener and Foxboro, based on populations of 180 000 and 100 residents, respectively (Table 4.7). The exact population of Foxboro is not known, but as stated in Section 4.4, the retirement community consists of 65 residences; as most residences are inhabited either by individuals or couples, it is reasonable to estimate the population at 100. Figure 4.6a illustrates the loading per person in the WWTP influents. The influent loading of caffeine is more than twice as high in Foxboro compared with Kitchener, and the influent loadings of sulfamethoxazole and trimethoprim are several orders of magnitude higher in Kitchener. The latter findings are difficult to explain; the former may be explained partly

Compound	Kitchener Effluent (g/day)	Kitchener Influent (g/day)	Foxboro Effluent (g/day)	Foxboro Influent (g/day)
Neutral Drugs				
Caffeine	75.0	432	0.12	1.9
Carbamazepine	40.0	19.3	0.0019	0.0070
Cotinine	7.32	122	0.015	0.023
Cyclophosphamide	0.4	1.1	N.D.	N.D.
Fluoxetine	1.0	1.0	N.D.	N.D.
Pentoxifylline	2	0.4	N.D.	N.D.
Trimethoprim	118	720	0.0085	0.00094
Acidic Drugs				
Bezafibrate	9.84	24.4	0.14	NA
Clofibric Acid	N.D.	N.D.	N.D.	NA
Diclofenac	7.3	17	0.015	NA
Fenoprofen	N.D.	N.D.	N.D.	NA
Gemfibrozil	5.2	10.1	0.16	NA
Ibuprofen	17	2.6×10^1	0.23	NA
Indomethacin	2.0×10^1	3	0.07	NA
Ketoprofen	N.D.	N.D.	N.D.	NA
Naproxen	58	106	0.17	NA
Sulfonamides				
Sulfacetamide	N.D.	N.D.	N.D.	N.D.
Sulfapyridine	1	12	0.0090	N.D.
Sulfadiazine	N.D.	N.D.	N.D.	N.D.
Sulfamethoxazole	183	1277	0.053	0.041
Sulfisoxazole	N.D.	N.D.	0.0001	0.0018
Sulfamethazine	N.D.	N.D.	0.00012	0.0014
Fluoroquinolones				
Ciprofloxacin	6.4	59	0.11	0.041
Norfloxacin	0.5	28	0.039	0.017
Ofloxacin	28	29	0.017	0.013

Table 4.6. Loading of PhACs in wastewater treatment plant influent and effluent, in Kitchener and Foxboro, measured in g/day. Note: ND = no pharmaceutical detected, so loading not calculated.

Compound	Kitchener Effluent (mg/person/day)	Kitchener Influent (mg/person/day)	Foxboro Effluent (mg/person/day)	Foxboro Influent (mg/person/d)
Neutral Drugs				
Caffeine	0.417	2.40	1.2	19
Carbamazepine	0.222	0.107	0.019	0.070
Cotinine	0.0407	0.676	0.15	0.23
Cyclophosphamide	0.002	0.00060	N.D.	N.D.
Fluoxetine	0.006	0.006	N.D.	N.D.
Pentoxifylline	0.01	0.002	N.D.	N.D.
Trimethoprim	0.656	4.00	0.085	0.0094
Acidic Drugs				
Bezafibrate	0.0547	0.136	1.4	NA
Clofibric Acid	N.D.	N.D.	N.D.	NA
Diclofenac	0.040	0.095	0.15	NA
Fenoprofen	N.D.	N.D.	N.D.	NA
Gemfibrozil	0.029	0.0563	1.6	NA
Ibuprofen	0.093	1.5	2.3	NA
Indomethacin	0.1	0.05	0.7	NA
Ketoprofen	N.D.	N.D.	N.D.	NA
Naproxen	0.32	0.587	1.7	NA
Sulfonamides				
Sulfacetamide	N.D.	N.D.	N.D.	N.D.
Sulfapyridine	0.007	0.069	0.090	N.D.
Sulfadiazine	N.D.	N.D.	N.D.	N.D.
Sulfamethoxazole	1.02	7.10	0.53	0.032
Sulfisoxazole	N.D.	N.D.	0.0010	0.02
Sulfamethazine	N.D.	N.D.	0.0012	0.014
Fluoroquinolones				
Ciprofloxacin	0.0036	0.33	1.1	0.41
Norfloxacin	0.003	0.16	0.39	0.17
Ofloxacin	0.16	0.16	0.18	0.13

Table 4.7. Per-person loading of PhACs in wastewater treatment plant influent and effluent, in Kitchener and Foxboro, measured in mg/person/day. Note: ND = no pharmaceutical detected, so loading not calculated; NA= not available due to analytical difficulties.
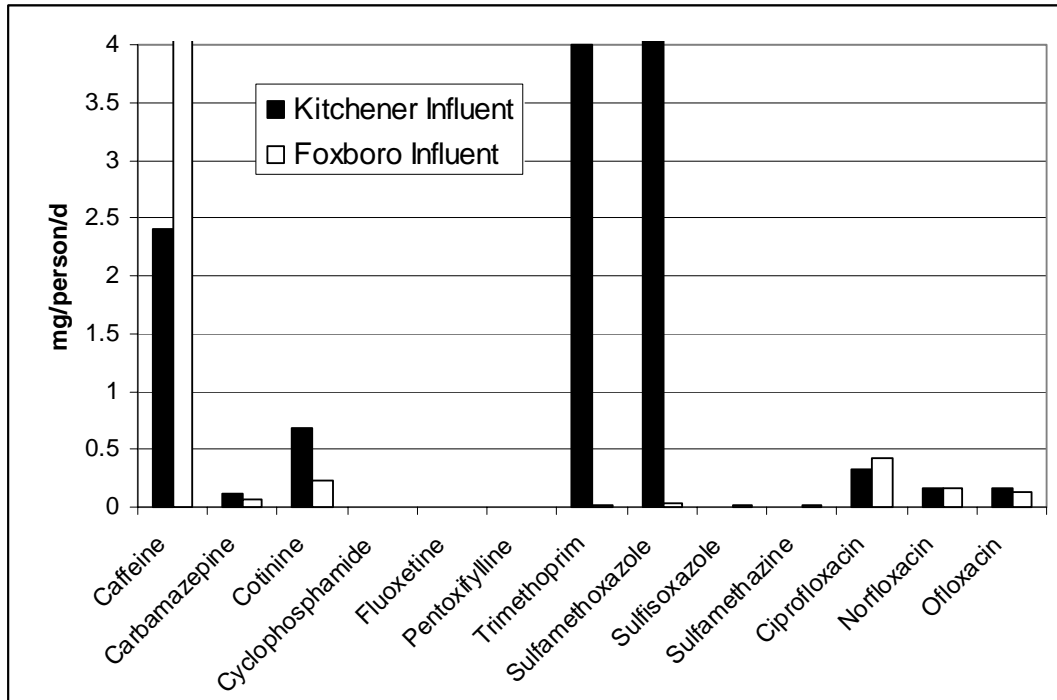
a)
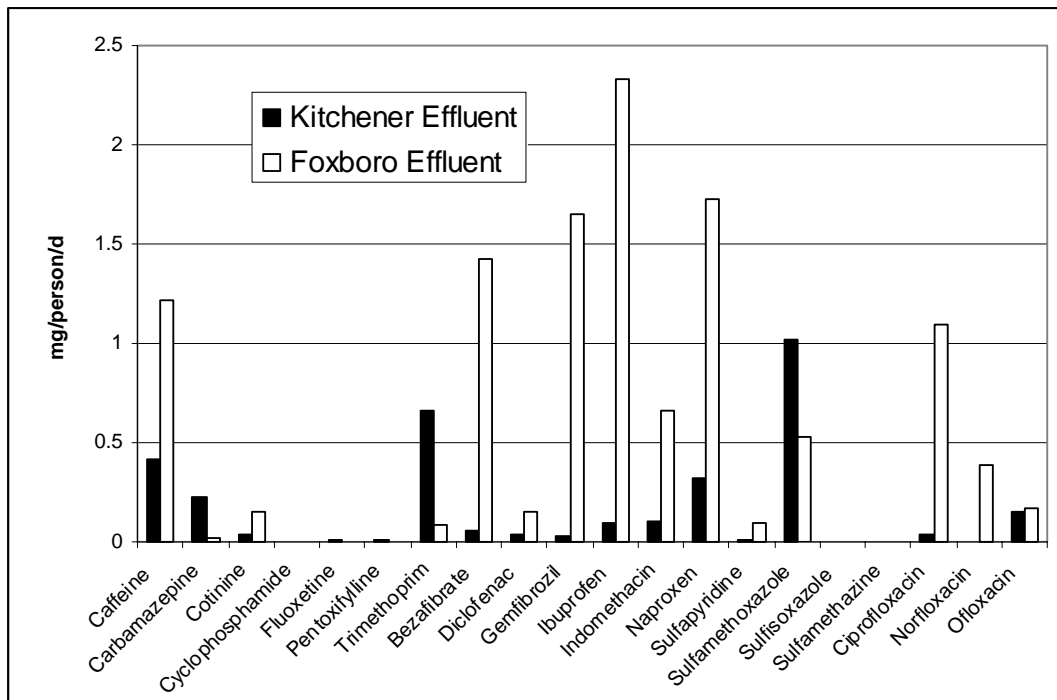
b)

Figure 4.6. PhAC loading per person in Foxboro and Kitchener, a) in influent, b) in effluent.

by differences in caffeine consumption. Interestingly, the per-person influent pharmaceutical loading is very similar for most PhACs in Foxboro and Kitchener, including for carbamazepine, cotinine, and the fluoroquinolone antibiotics. However, a different picture is evident when examining the per-person PhAC loading in the effluent (Fig. 4.6b). With the exception of the anomalously high trimethoprim and sulfamethoxazole loadings, the per-person environmental loading of pharmaceuticals is much lower in Kitchener than in Foxboro. In general, the per-person loading of pharmaceuticals to the environment is one order of magnitude higher in Foxboro than in Kitchener. Interestingly, a study of per-person pharmaceutical loading in Ontario WWTP effluent by Lishman et al. (2006) yielded median values greater than the loading from the Kitchener plan, but below the loading values for Foxboro as determined here. In summary, the total daily loading of pharmaceuticals to the environment is several times greater at the Kitchener WWTP than Foxboro. However, the contribution of each person to the loading of PhACs to the environment is an order of magnitude higher in Foxboro than in Kitchener.

Removal rates for PhACs in WWTPs are helpful in understanding whether or not upgrading wastewater treatment plants would reduce the release of PhACs to the environment. Unfortunately, it is not possible to definitively determine a removal rate for pharmaceuticals in WWTPs, as retention times within WWTPs vary, such that composition of effluent does not necessarily reflect the composition of influent (Metcalfe, Koenig et al., 2003). However, the difference between the concentrations of PhACs in the WWTP influent and effluent, accounting for the total plant retention time, can be calculated and can be used to estimate removal rates. Table 4.8 lists the differences between influent and effluent concentrations for detected PhACs. Figures 4.7, 4.8 and 4.9 illustrate these differences for the Foxboro and Kitchener WWTPs. Where negative percentages (<0) are found, influent concentrations are measured as being higher than effluent concentrations. This may be due to analytical difficulties, or may be due to de-conjugation of pharmaceutical glucuronides in wastewater treatment plants. Pharmaceutical conjugates are not detected in the analysis, so de-conjugation to the parent PhAC in WWTPs may give the appearance of an increase in total concentration (Baronti et al., 2000). The average difference between influent and effluent

concentrations was 51% for the Kitchener plant, which is similar to the value of 60% reported by Ternes (1998). For the Foxboro plant, the difference between influent and effluent concentrations was 35%. The concentrations of fluoroquinolone antibiotics in the Foxboro effluent were no lower than in the influent, suggesting that the plant may not be effectively removing the pharmaceuticals. This is further supported by other data suggesting relatively poor performance of the Foxboro plant in general (Table 4.1, Section 4.4.2). Lindberg et al. (2006) found that 97% and 96% of norfloxacin and ciprofloxacin were removed, respectively, by a secondary, activated sludge WWTP. Accordingly, the poor removal of antibiotics in the Foxboro plant is likely due to sub-optimal plant operation. Because influent concentrations of acidic drugs could not be

PhAC	Kitchener % Difference	Foxboro % Difference
Bezafibrate	60	NA
Caffeine	83	94
Carbamazepine	<0	73
Ciprofloxacin	89	<0
Cotinine	94	36
Cyclophosphamide	67	ND
Diclofenac	58	NA
Fluoxetine	5	ND
Gemfibrozil	49	NA
Ibuprofen	94	NA
Indomethacin	<0	NA
Ketoprofen	45	NA
Naproxen	89	<0
Norfloxacin	98	<0
Ofloxacin	5	<0
Pentoxyfilline	<0	ND
Sulfamethazine	ND	92
Sulfamethoxazole	86	<0
Sulfisoxazole	ND	95
Trimethoprim	84	<0
Mean	*51*	*35*

Table 4.8. Differences between effluent and influent concentrations of PhACs detected at the Foxboro and Kitchener WWTPs. NA: not available (due to analytical difficulties); ND: not detect in influent or effluent.
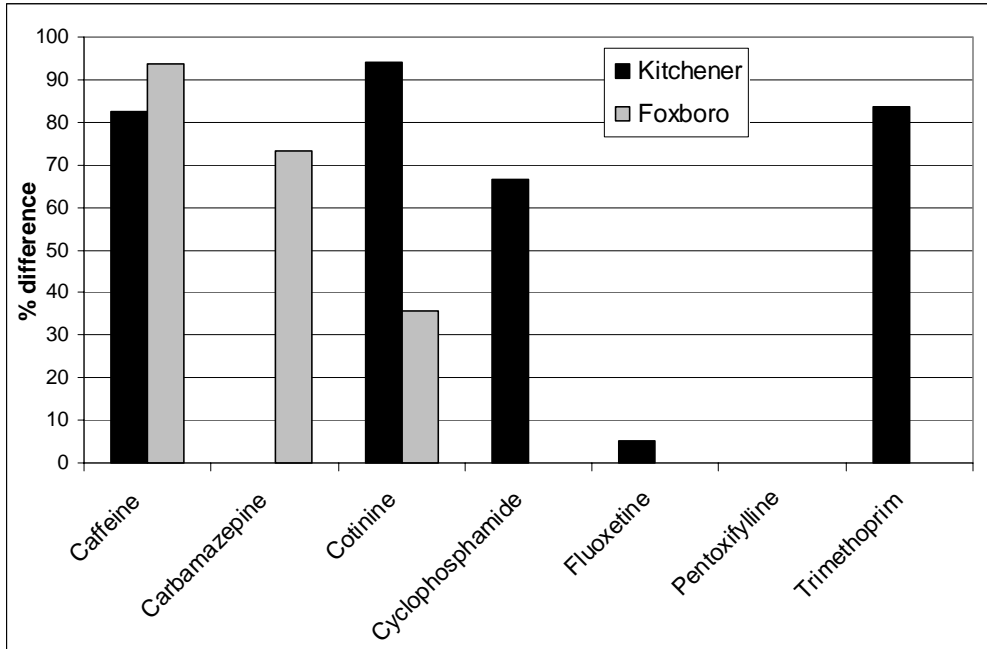
Figure 4.7. Difference between influent and effluent concentrations of neutral drugs in the Kitchener and Foxboro WWTPs.
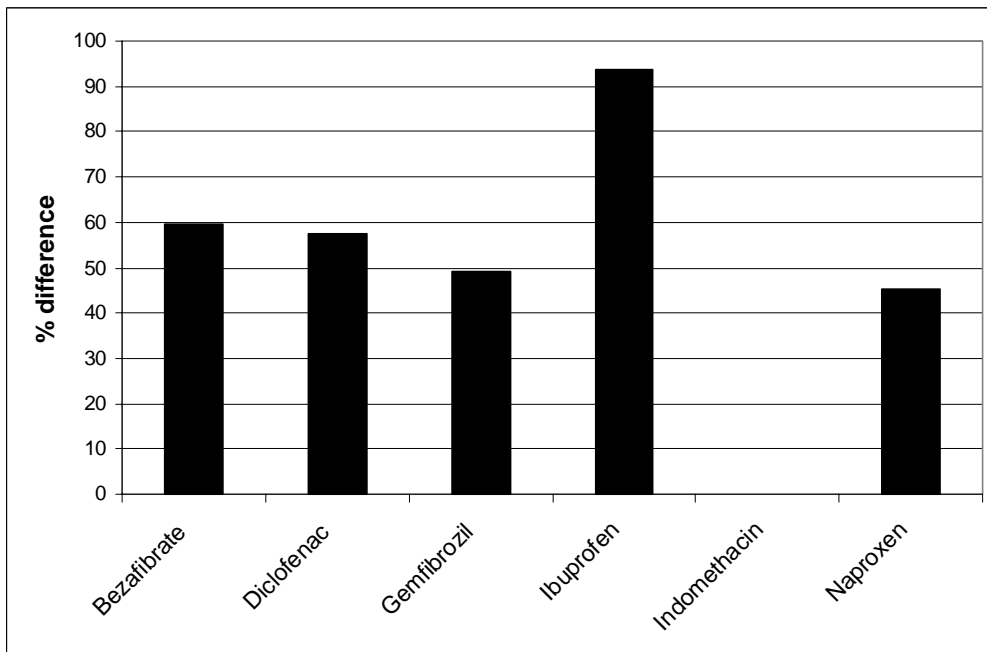
Figure 4.8. Difference between influent and effluent concentrations of acidic drugs in the Kitchener WWTP.
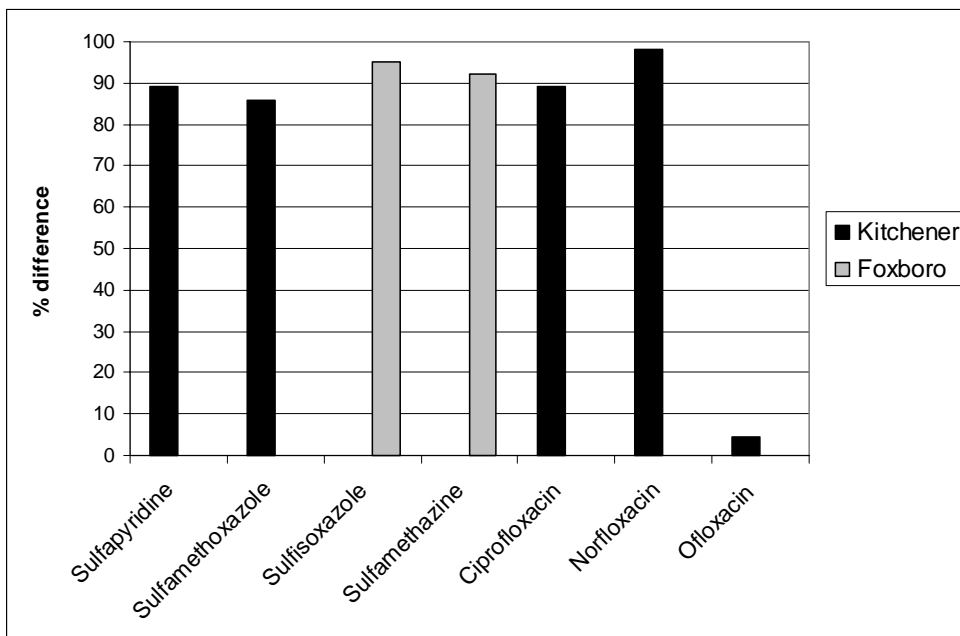
Figure 4.9. Difference between influent and effluent concentrations of antibiotics in the Kitchener and Foxboro WWTPs.

measured, it is difficult to comment on whether poor plant performance also contributed to the high effluent concentrations of acidic and neutral drugs for the Foxboro plant. However, this result would not be surprising given similar findings in the literature (Clara et al., 2005; Vieno et al., 2005).

The high concentrations of sulfamethoxazole in the Kitchener effluent are difficult to explain, as the difference between the influent and effluent is 86%, suggesting relatively effective removal by the plant. Furthermore there is no known reason why the Kitchener plant might be receiving a greater loading of sulfamethoxazole than other plants. The moderate to high concentrations of pharmaceuticals being released to groundwater by the Foxboro plant, and to the Grand River by the Kitchener plant do suggest that the Waterloo Region is an appropriate location for management action to reduce the release of pharmaceuticals to the environment. Management action will be most effective if it is focused on locations releasing high concentrations of pharmaceuticals to the environment.

4.5.2 Social surveys

The social surveys included a variety of questions related to the management of pharmaceuticals in the local environment. Because consumption of pharmaceuticals is the main contributor to the environmental loading of PhACs, respondents were asked about their frequency of pharmaceutical usage (Appendix C). Respondents over 60 reported consuming greater quantities of pharmaceuticals than other age groups. Seniors in the Kitchener survey consumed at least 30% more pharmaceuticals than other age cohorts in that location, and approximately 20% more prescription pharmaceuticals than those in the Foxboro community (Fig. 4.10). This observation may be partly related to socioeconomic differences. For example, the education level in Foxboro is somewhat higher than in Kitchener (Fig. 4.11), suggesting a higher socioeconomic status. Furthermore, the Foxboro retirement community is a relatively affluent community compared with the Kitchener location where the survey was conducted. Although seniors consumed more pharmaceuticals such as cholesterol, heart, blood pressure and pain medication, younger respondents generally consumed more hormones and antibiotics (Fig. 4.12). Antibiotics were among the PhACs whose concentrations were highest in the Kitchener WWTP effluent, and as the synthetic hormone 17α-ethinylestradiol
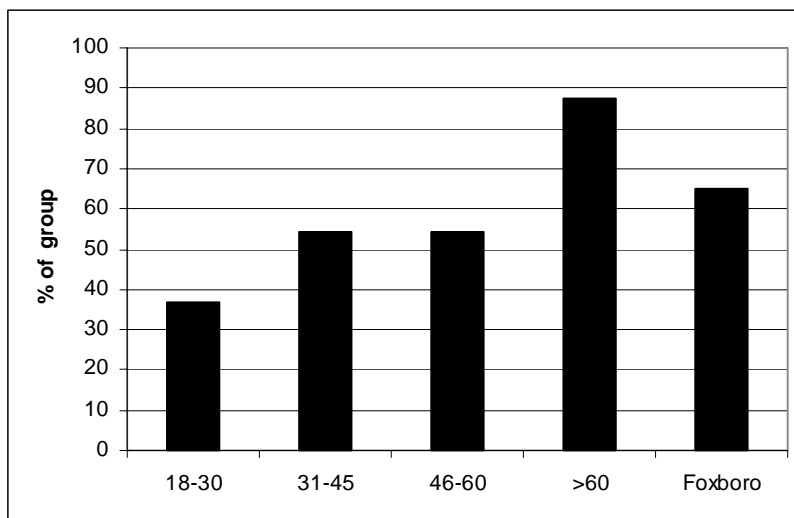
Figure 4.10. Daily prescription use by survey respondents in Kitchener and Foxboro. Graph illustrates the percentage of each age group from the Kitchener survey, and of the Foxboro respondents, who reported taking daily prescription medications.
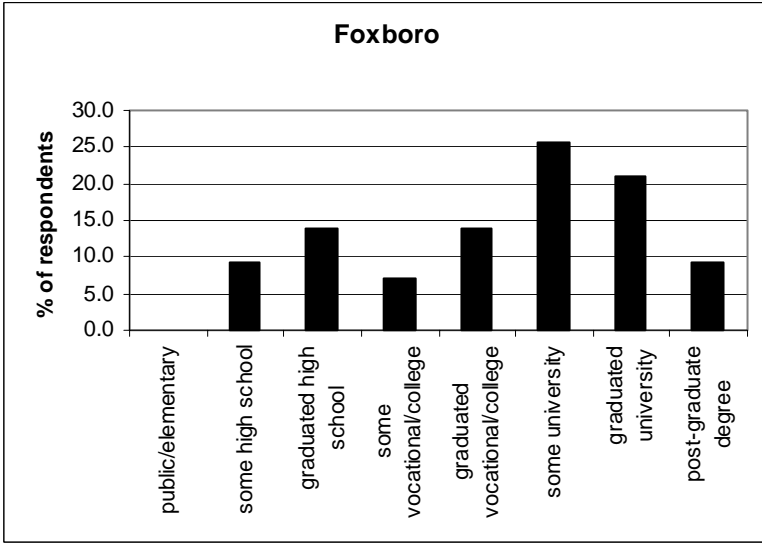
Figure 4.11. Levels of education of respondents in surveys in Kitchener and Foxboro.
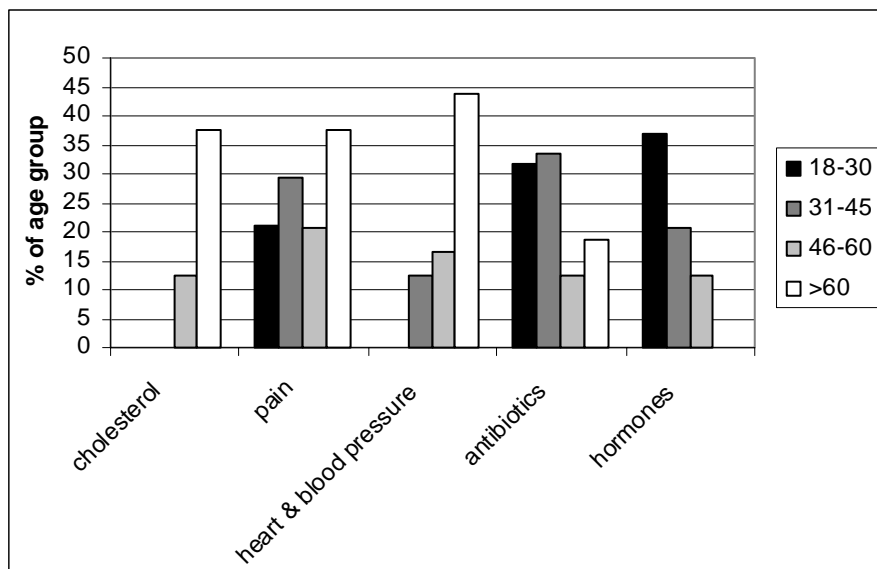
Figure 4.12. Consumption of medications by age group in Kitchener survey. Graph illustrates the percentage of each age group who consumed a given type of medication within the past year.

is the PhAC for which effects have been most clearly demonstrated on aquatic organisms. Therefore the findings of high antibiotic and hormone usage rates among youth suggest that consumption of pharmaceuticals by younger age groups should not be underestimated as a contributor to environmental impacts by PhACs.

In Kitchener, antibiotics and pain medication were among the prescription medications most frequently used (Fig. 4.13). When prescription medications taken on a daily basis were considered, pain medication, heart and blood medication, and hormones were most abundant (Fig. 4.14). In Foxboro, cholesterol and heart and blood medications were consumed by the greatest number of respondents on a daily basis (Fig. 4.14), with pain medication, cholesterol, and heart and blood pressure medication being most abundant among the medications consumed in general (not only on a daily basis) (Fig. 4.13). Pain medications, together with herbals and vitamins, were the non-prescription medications consumed by the greatest number of respondents in both Kitchener and
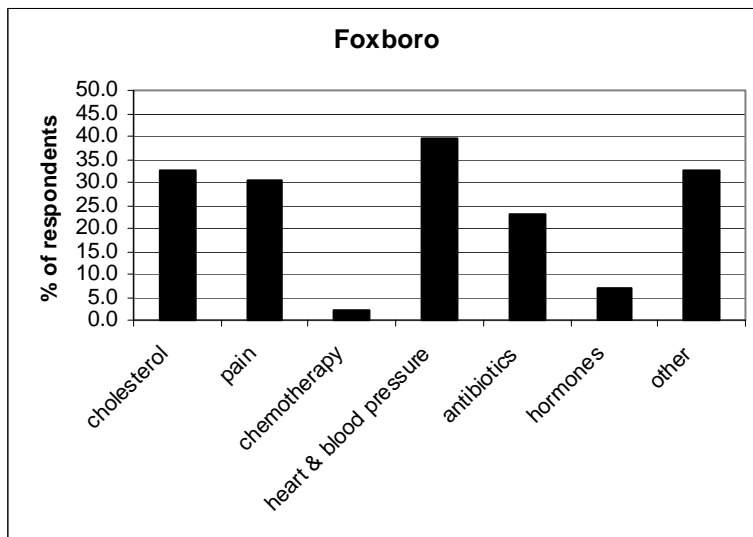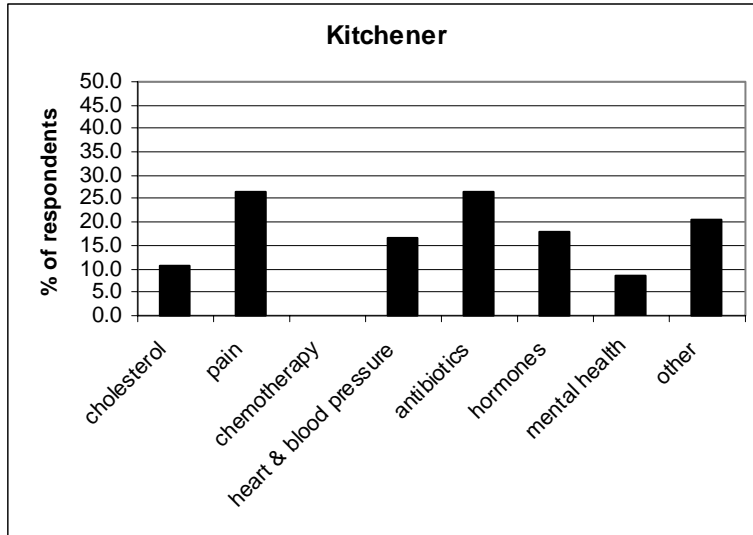
Figure 4.13. Percentages of respondents from Kitchener and Foxboro reporting having taken a given prescription medication over the past year.
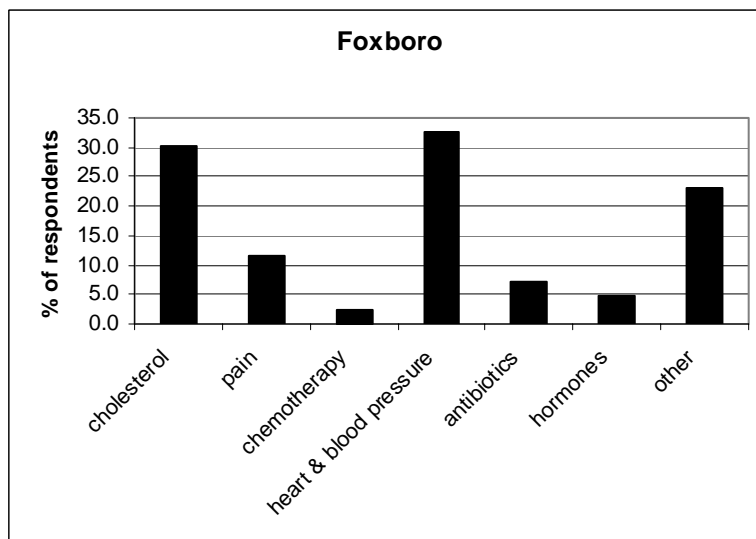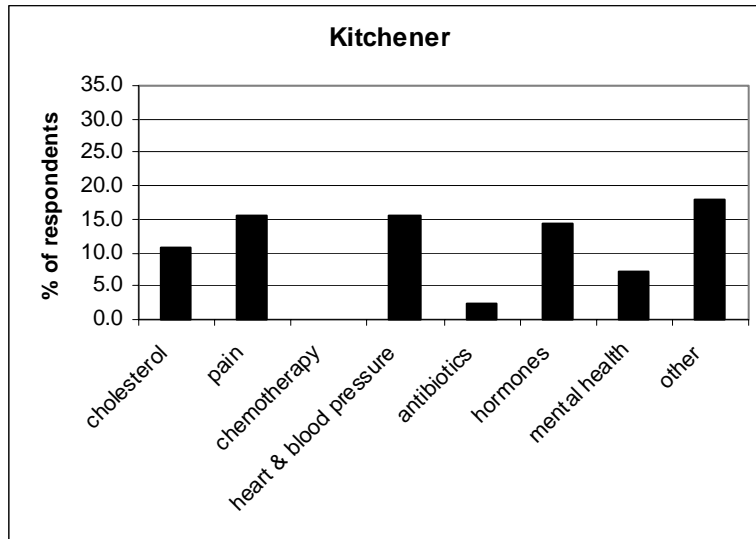
Kitchener

Foxboro

Figure 4.14. Percentages of respondents from Kitchener and Foxboro reporting taking a given prescription medication on a daily basis.

Foxboro (Figs. 4.15, 4.16). In both communities, acetaminophen was the non-prescription medication consumed by the most respondents, with 42% and 20% of the Kitchener and Foxboro respondents, respectively, having taken it over the past year (Fig. 4.15). On a daily basis, herbals and vitamins were taken by the most respondents, followed by ASA (acetylsalicilic acid) (Fig. 4.16). Ibuprofen was the third most commonly used non-prescription pain medication (Figs. 4.15, 4.16). These consumption patterns are similar to those in other countries. For example, in Australia, acetaminophen

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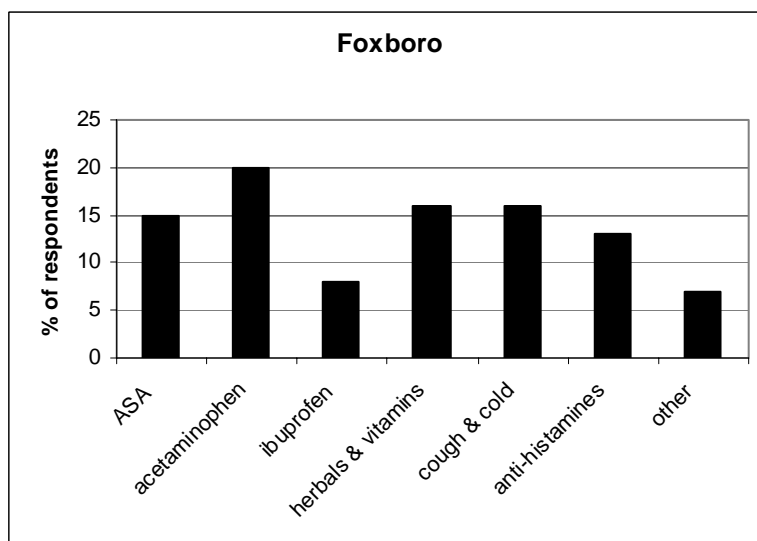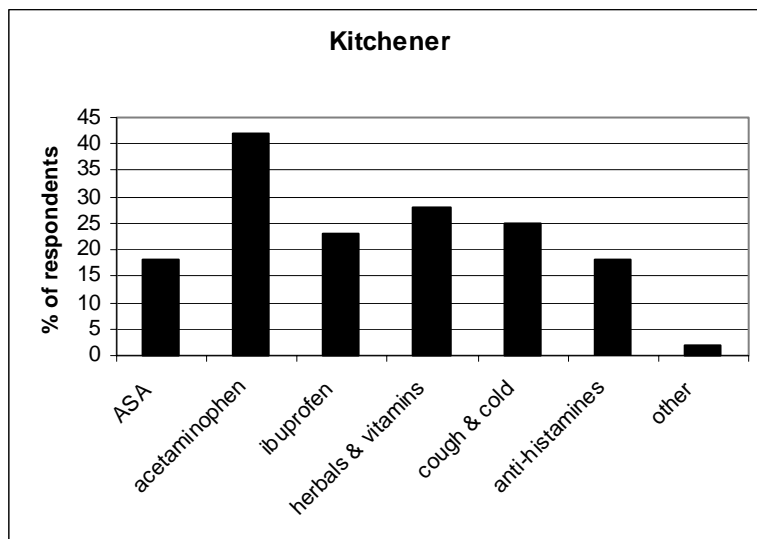
Kitchener

Foxboro

Figure 4.15. Percentages of respondents from Kitchener and Foxboro reporting having taken a given non- prescription medication over the past year.

(also known as paracetamol) is the most dispensed medication by mass, while acetylsalicylic acid and ibuprofen are the 9th and 10th most frequently dispensed (Khan & Ongerth, 2004). Despite being consumed less frequently than acetaminophen or ASA, however, ibuprofen may represent a greater environmental concern, as there are indications that it persists in the environment longer than than ASA or acetaminophen (Lee et al., 2004).
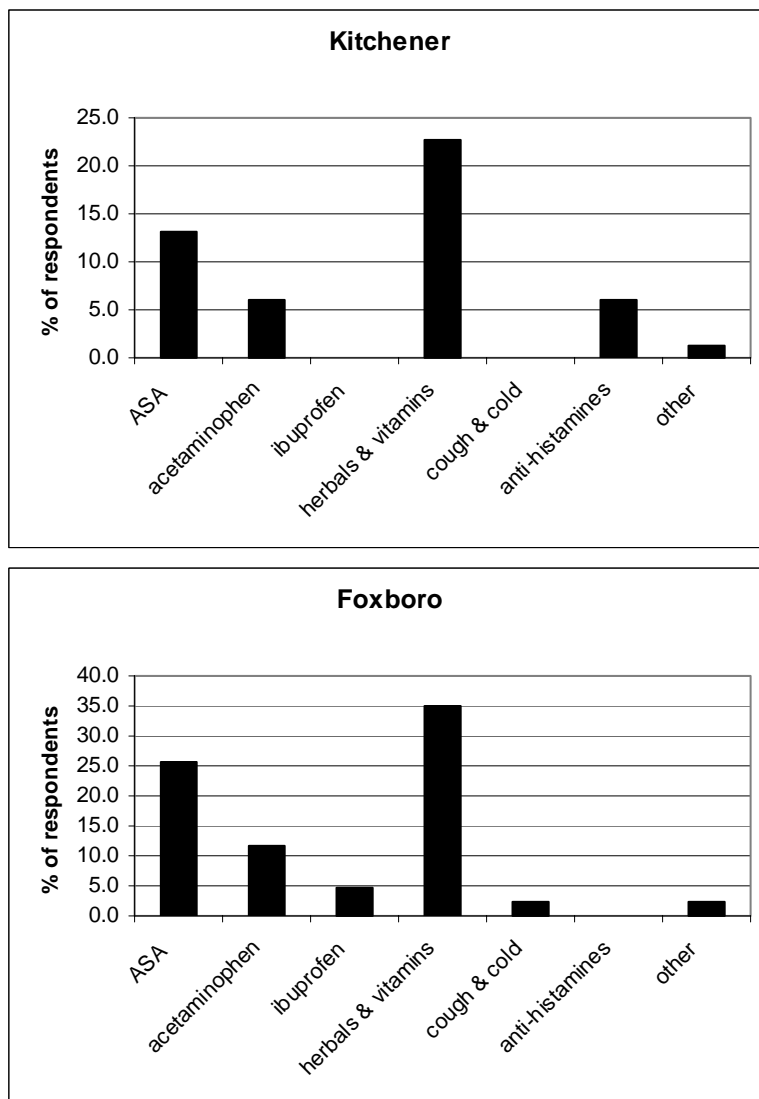
Figure 4.16. Percentages of respondents from Kitchener and Foxboro reporting taking a given non-prescription medication on a daily basis.

Although improper disposal of pharmaceuticals is also a mechanism causing environmental contamination by PhACs, it is believed to be a minor contributor compared with consumption and excretion (Heberer, 2002a; Reddersen, Heberer, & Dünnbier, 2002). Nevertheless, some estimates suggest that as much as 1/3 of domestic pharmaceuticals are disposed of as waste, in the toilet or garbage (Greiner & Rönnefahrt, 2003). The results of the surveys support the view of disposal as a relatively minor contributor to the environmental loading of PhACs. Most respondents reported disposing of medications rarely: either yearly or almost never (Fig. 4.17). However, of those who
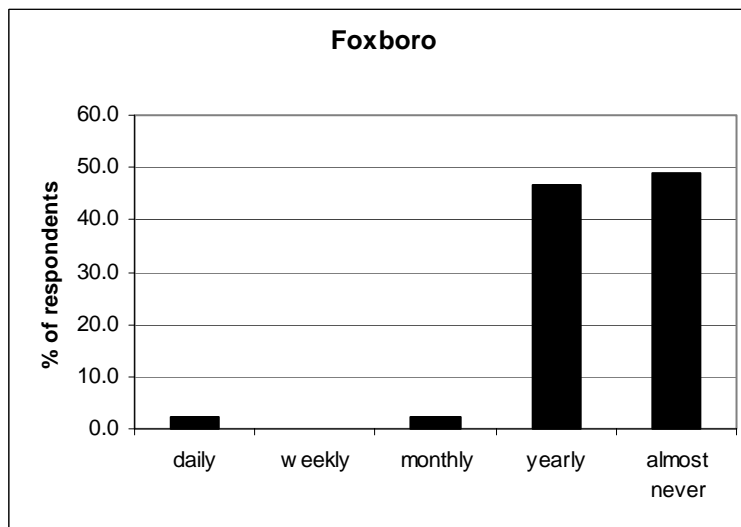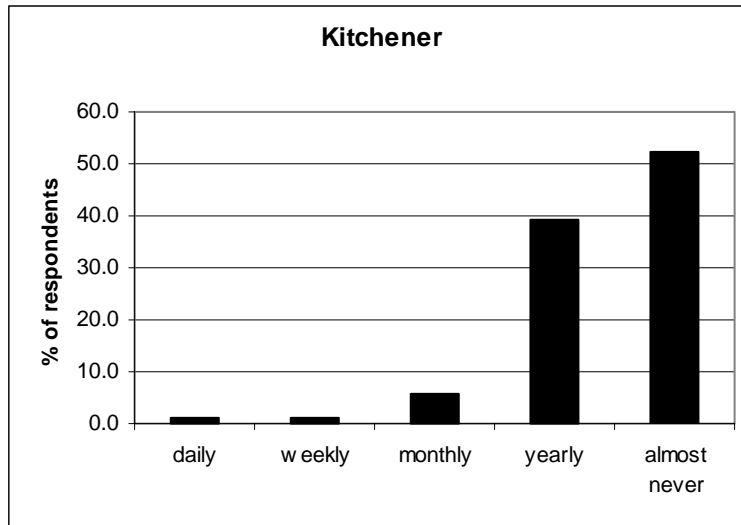
Figure 4.17. Frequency with which survey respondents dispose of their unused/expired medications.

did dispose of unused or expired pharmaceuticals, many did not do so properly. In Kitchener, 55% of respondents put their pharmaceuticals in the garbage and 20% flushed them down the toilet (Fig. 4.18). In Foxboro, 35% of respondents put pharmaceuticals in the garbage and 23% put flushed them down the toilet (Fig. 4.18). These results are similar to the results of a study by COMPAS for Health Canada (2002), which found that 50% and 39% of Canadians dispose of non-prescription and prescription drugs, respectively, in the garbage and that 19% and 20% of prescription and non-prescription

Kitchener

Foxboro
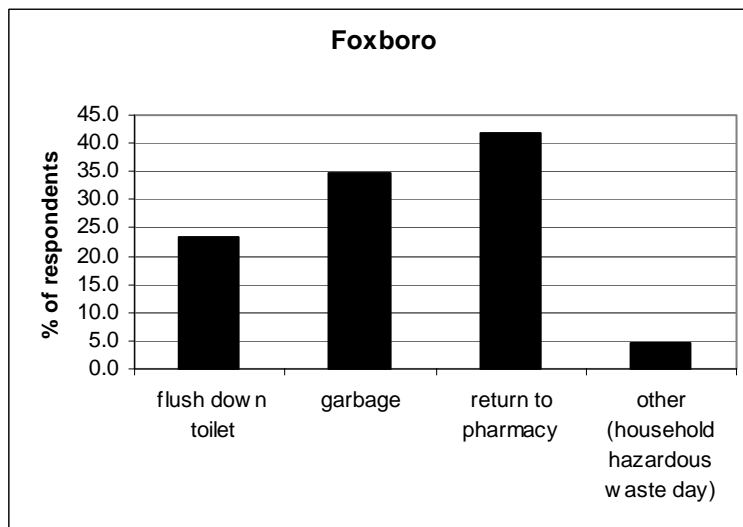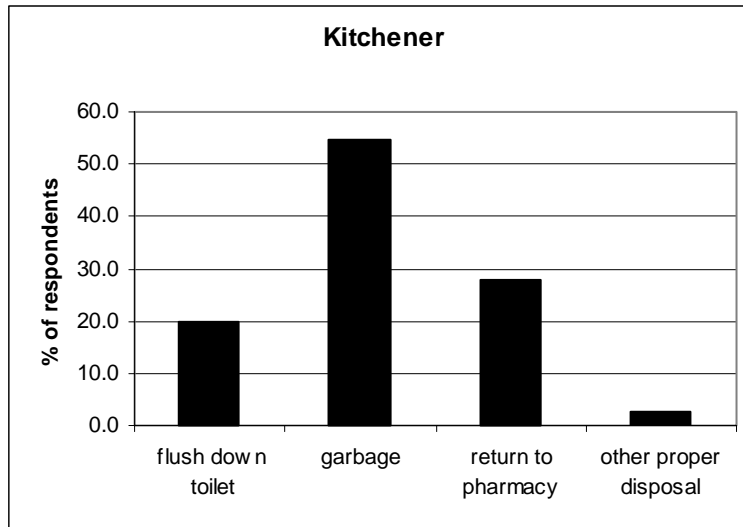
Figure 4.18. Methods used by respondents to dispose of unused or expired medications.

drugs are disposed in the toilet or sink. In a study conducted in the U.K., 63.2% of respondents placed medications in the garbage, 11.5% in the sink or toilet, and 21.8% returned them to the pharmacy (Bound, Kitsou, & Voulvoulis, 2006). Garbage disposal rates in an American study were 54% (Kuspis & Krenzelok, 1996), and the rate of disposal via toilet was 35.4%. This toilet disposal rate is higher than in the current study, or the studies in Canada and the U.K. mentioned above (Bound et al., 2006; Compas for Health Canada, 2002). The American study was conducted a decade before this study and the issue of pharmaceuticals in the environment received little attention before the mid-1990s. This may partially explain the differences in pharmaceutical disposal

methods, such as the rates of toilet disposal. Both garbage and toilet disposal provide a pathway for PhACs to enter the aquatic environment. Toilet disposal ultimately leads to contamination of WWTPs and landfills potentially contaminate groundwater where no liner and leachate collection exists. Where leachate is collected, it is usually sent to WWTPs for treatment (pers. comm., D. Andrews).

Proper disposal of pharmaceuticals entails returning pharmaceuticals to the pharmacy, where they will be sent for incineration, and actions which prevent the pharmaceuticals from entering the environment, such as bringing them to a hazardous waste disposal day. Incineration effectively destroys pharmaceuticals and has extremely low atmospheric emissions (Bridges, Bridges, & Potter, 2000; Porteous, 2001). In Kitchener, 28% of respondents said they returned their unused or expired medications to the pharmacy, a rate slightly higher than the 21.8% return rate found in the U.K. by Bound et al. (2006). Three percent of respondents disposed of pharmaceuticals properly in a different way. In Foxboro, the rate of proper disposal was higher; 42% of respondents returned unused medications to the pharmacy and 5% to hazardous waste day. Because of the relatively large difference between the results for Foxboro and Kitchener, the disposal methods reported in the Kitchener survey were classified by age group, to assess whether the age of the Foxboro respondents might be related to disposal rate. The data illustrated that the rate of proper disposal increased with age. Fifty percent of seniors in the Kitchener survey properly disposed of their pharmaceuticals, whereas only 6% of respondents between ages 18-30 properly disposed of their unused or expired medications (Fig. 4.19). However, the percentage of each age group who put medications in the toilet increased with age (Fig. 4.19). Younger respondents were much more likely to dispose of pharmaceuticals in the garbage (89% for ages 18-30) than in the toilet (6% for ages 18-30), whereas seniors were more likely to put pharmaceuticals in the toilet (33%) than in the garbage (25%). The reason for the increasing rate of toilet disposal with age is likely that, in North America, residents were told in previous decades that they should dispose of pharmaceuticals in the toilet, so that children could not consume them and be poisoned (Kuspis & Krenzelok, 1996). Older respondents are more likely to have received the 'toilet disposal' message in the past. Younger respondents were likely never told to put medications in the toilet, as the 'toilet disposal'
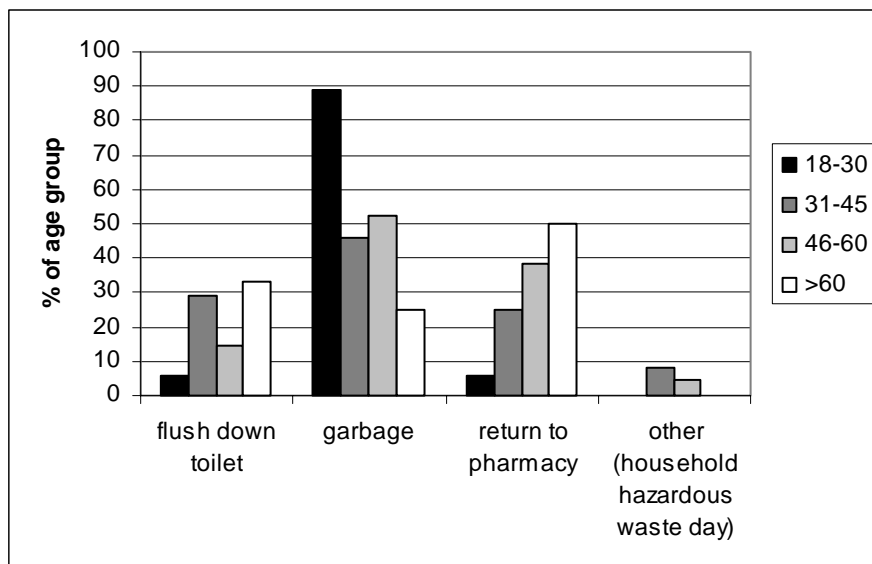
Figure 4.19. Methods of disposal of unused and expired medication by age group in Kitchener.

message has now been replaced with advice to return medications to the pharmacy, for environmental reasons. The reason why the younger respondents are less diligent in returning medications to the pharmacy than older respondents, however, is more difficult to assess. Possible reasons include a lack of awareness of the issue of pharmaceuticals in the environment, of the possibility of returning drugs to the pharmacy, or attitudes differing from those of older respondents.

Respondents were asked whether or not they were aware that water contamination by pharmaceuticals was an environmental concern, and whether or not they were aware that pharmaceuticals could be returned to the pharmacy for disposal. In Kitchener, 49% of respondents were aware of the issue of pharmaceuticals in the environment; in Foxboro, the number of respondents aware of the issue was higher, at 62%. The findings in Kitchener are very similar to those in the study by Bound et al. (2006), where just over half of their U.K. respondent felt that pharmaceuticals could be harmful to the environment.   In Kitchener, 42% of respondents knew that they could return unused or expired medications to the pharmacy; in Foxboro, the number was 58%. Again, the results were examined to see if age might have contributed to the difference between Foxboro and Kitchener. Awareness that unused or expired drugs could be returned to the

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pharmacy did increase with age, with 63% of seniors in Kitchener saying they knew of this disposal method, whereas only 16% of those aged 18-30 were aware of it (Fig. 4.20). However, awareness of the issue of pharmaceuticals in the environment was somewhat less age dependent; although seniors in Kitchener were again the group displaying the greatest awareness, at 63%, 53% of the youngest respondents had also heard about pharmaceuticals polluting water (Fig. 4.21). The group least aware of this environmental issue was the 31-45 year olds, at 33%. It may be that young people have recently heard about pharmaceuticals in the environment through educational institutions which some attend, such as colleges and universities, explaining their relative awareness of the issue. Their lack of awareness that pharmaceuticals can be returned to the pharmacy for disposal may be because they use relatively few medications (Fig. 4.10), are therefore less likely to be at a pharmacy or interact with a pharmacist, and are thus less likely to receive information regarding disposal, than seniors. This lack of awareness may partly explain the poor drug disposal habits of the younger age group.

To ascertain whether or not increasing awareness through education programs might enhance the rate of proper drugs disposal, the responses of those who said they knew pharmaceuticals could be returned to the pharmacy for disposal were compared with the actual disposal methods used. In Kitchener, 54% of respondents who knew it was possible to return unused medications to the pharmacy did so (Fig. 4.22). Seventy-seven percent of the respondents who were aware both that pharmaceuticals represented an environmental concern and that it was possible to return unused drugs to the pharmacy did so. In Foxboro, however, awareness of the issue of pharmaceuticals in the environment did not improve disposal behaviour. Seventy-four percent of Foxboro respondents who were aware that unused medications could be returned to the pharmacy did so, whether or not they were aware that pharmaceuticals represented an environmental concern. Of those who did know that water pollution by pharmaceuticals was a concern, 69% returned their unused medications to the pharmacy (Fig. 4.22). Thus Foxboro residents appear to be returning medications to the pharmacy as a general practice, rather than because of a specific environmental concern, to a greater degree than Kitchener respondents. This may again be linked to the age difference in the
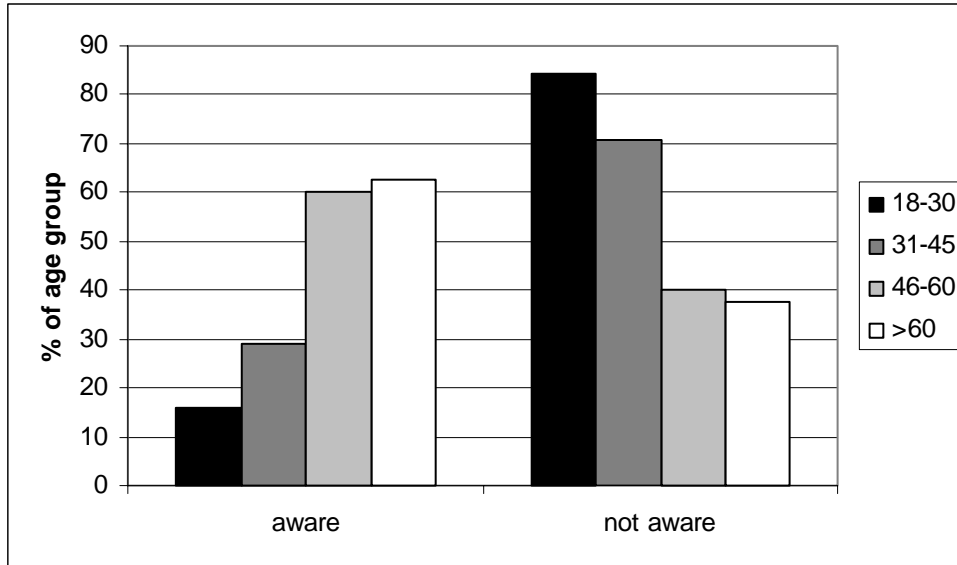
Figure 4.20. Awareness of Kitchener respondents that unused or expired medications could be returned to the pharmacy for disposal, according to age group.
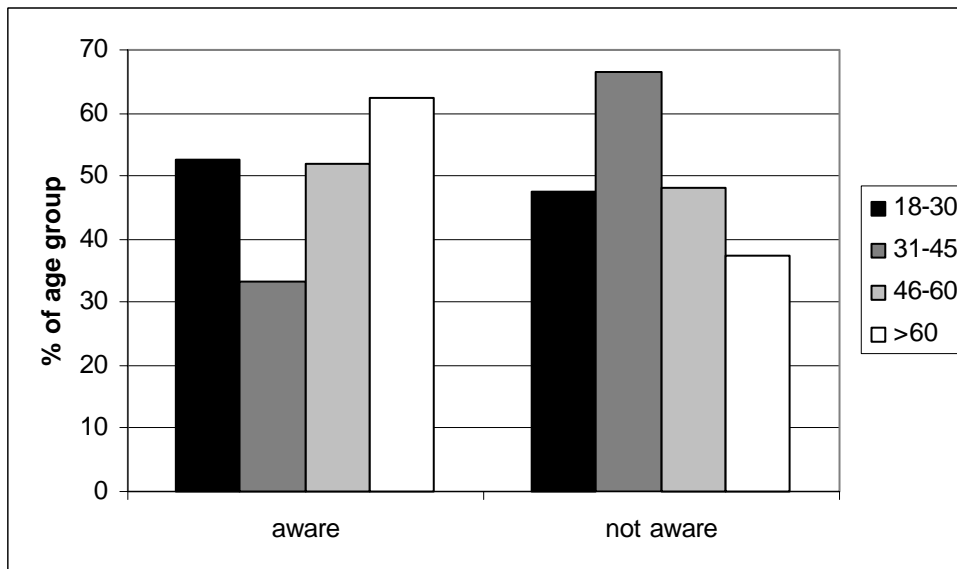
Figure 4.21. Awareness of Kitchener respondents that water pollution by pharmaceuticals is an environmental concern.

Kitchener

Foxboro
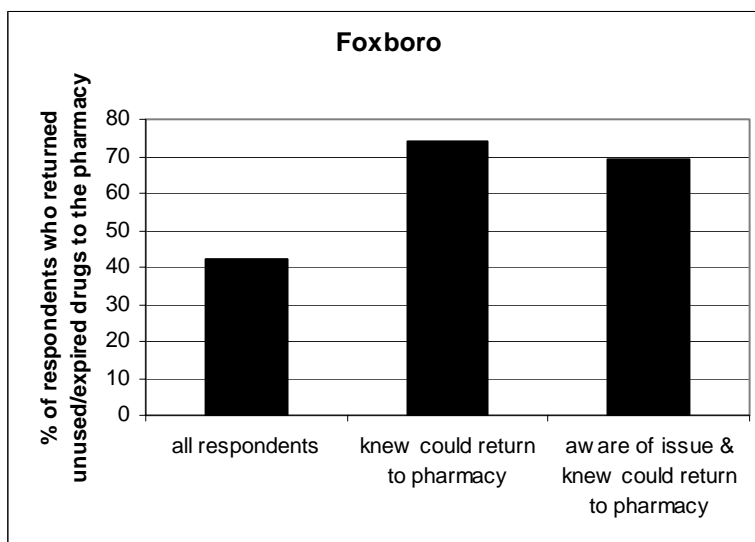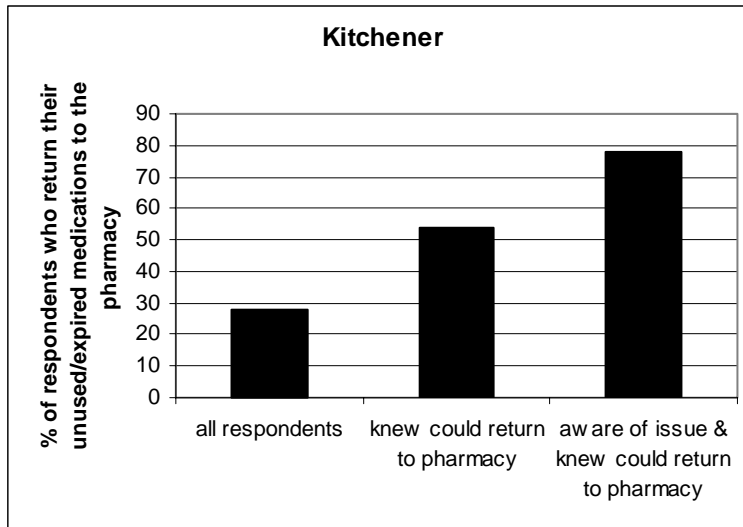
Figure 4.22. Disposal behaviour of respondents according to awareness of the possibility of returning unused/expired medications to the pharmacy, and awareness of the issue of pharmaceuticals in the environment.

communities, with the Foxboro seniors consuming more pharmaceuticals and therefore visiting the pharmacy more often. Possibly returning unused or expired medications may be more convenient and more likely to become a habit of the cohort.

To determine whether inconvenience might be a barrier to the return of unused and expired medications to the pharmacy, respondents were asked how inconvenient it would be to return their medications to the pharmacy for disposal. The majority did not

feel the practice would be inconvenient (Fig. 4.23). Eighty-one percent of Foxboro respondents, and 73% of Kitchener respondents disagreed strongly or somewhat with the statement, "Returning my unused or expired medication to the pharmacy for disposal would be inconvenient." In Foxboro, 74% strongly disagreed that returning medications to the pharmacy was inconvenient, compared with 44% in Kitchener. This supports the theory that Foxboro respondents return their unused drugs due to habit, because of convenience. This may explain why awareness of the issue of PhACs in the environment appears to play a lesser role in the disposal habits of Foxboro respondents than Kitchener
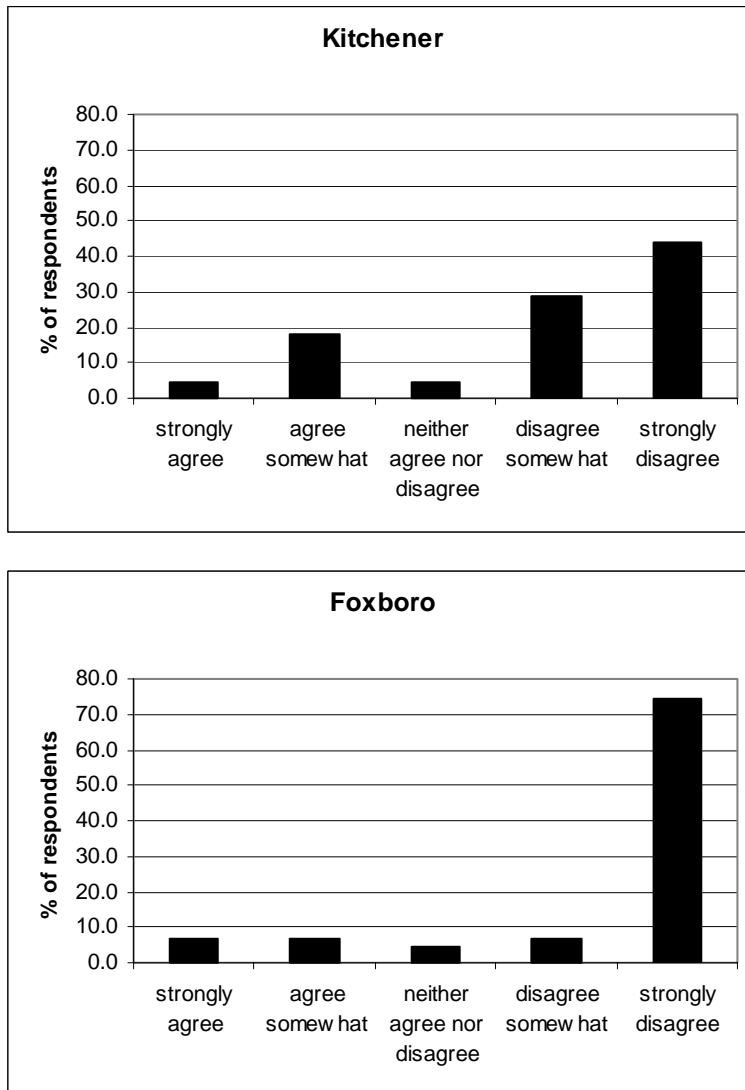
Figure 4.23. Responses to the statement, "Taking my unused or expired medication to the pharmacy for disposal would be inconvenient."

respondents. In comparison with a survey by Compass for Health Canada, respondents in both locations were more likely to disagree that returning medications to the pharmacy for disposal was inconvenient; 63% disagreed in the Likert-style question asked in the Compas survey for Health Canada (2002). However, the results of the Kitchener survey may have been influenced by the presence of a pharmacy in the plaza where the survey was being conducted. This may have resulted in fewer respondents feeling that bringing medications back to the pharmacy was inconvenient.

In addition to asking about respondents' attitudes specifically related to the disposal of pharmaceuticals, attempts were made to assess their attitudes towards the protection of the environment in general. The purpose of this question was to get a sense as to whether or not respondents would like to see management action taken to address an environmental issue such as pharmaceuticals in the environment. The approach of trying to ascertain respondents' attitudes towards an issue 'such as' PhACs in the environment was used because residents were not expected to have in-depth knowledge of the problem of environmental contamination by PhACs, and teaching each respondent about the details of the issue would have been too time-consuming. Instead, respondents were asked about general environmental problems with similar characteristics to PhACs issue, such as a greater risk to ecosystem health than human health (See Appendix C, questions 8-10). Respondents generally exhibited attitudes strongly in favour of managing problems such as pharmaceuticals in the environment. They felt that all water contamination should be mitigated, even if the effect of the contamination was unclear; they were concerned about problems which only affected ecosystem health, not human health; and they were concerned about environmental problems which did not affect them directly (Fig. 4.24, 4.25, 4.26). Respondents generally ranked the environment as their second priority in a broad list of concerns, below human health but above education or jobs (Table 4.9). However, the eagerness for management to address water contamination was considerably more muted when financial considerations were introduced. When asked how much they would be willing to pay to reduce water contamination by
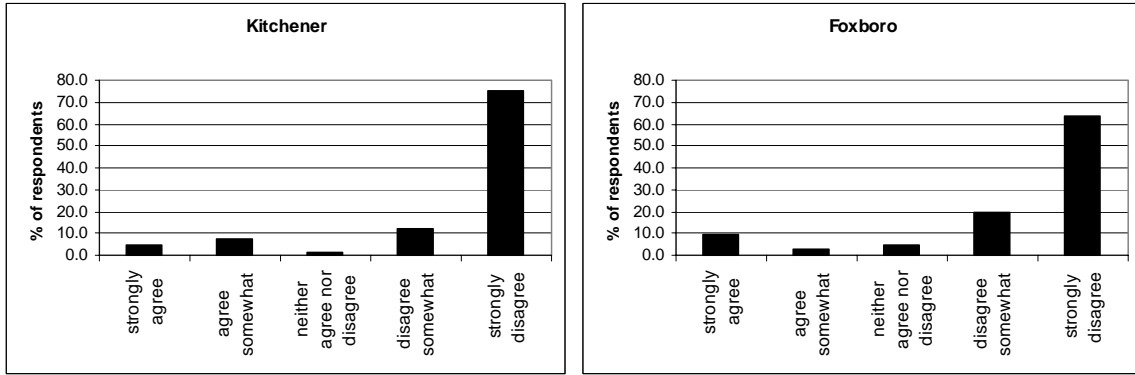
Figure 4.24. Responses to the statement, "We should only spend money on environmental problems that affect human health, not on problems that only affect other species or ecosystems."
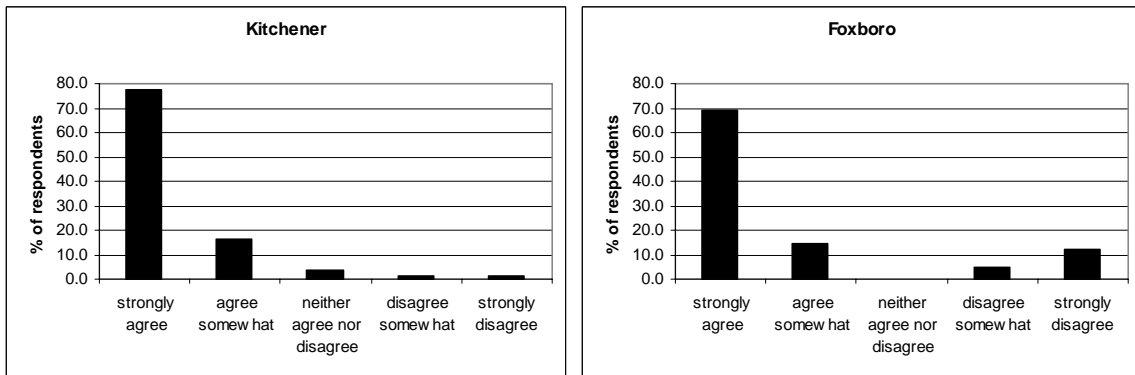
Figure 4.25. Responses to the statement, "We should try to prevent all water pollution, even if we have no evidence that a pollutant will harm human or ecosystem health."
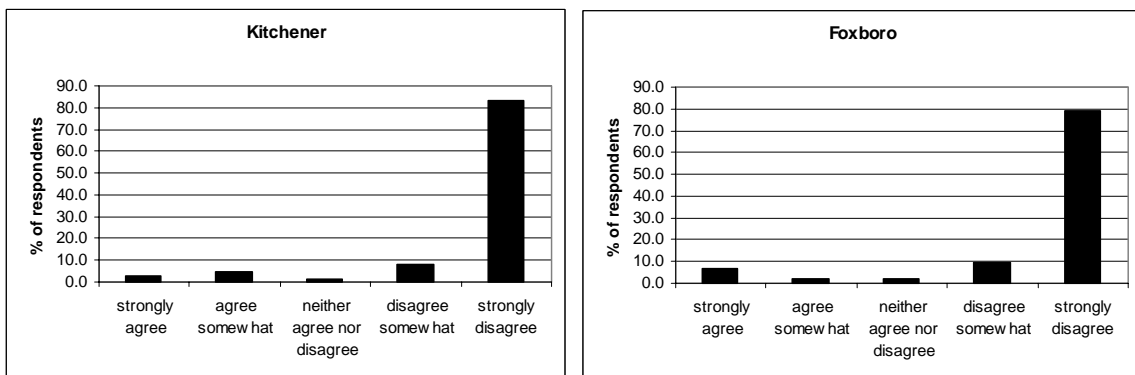
Figure 4.26. Responses to the statement, "If an environmental problem doesn't affect my health or my property, I don't care about it."

Concern	Kitchener	Foxboro
Human health	1.3	1.1
Environment	2.4	2.2
Education	2.7	2.9
Jobs	3.7	3.8
Transportation	4.5	4.6

Table 4.9. Aggregated rankings of concerns in order of importance to respondents, with a score of 1 representing the most important concern.

pharmaceuticals through sewage treatment and to generally improve environmental quality by upgrading WWTPs, the responses in both Foxboro and Kitchener were much more mixed (Fig. 4.27). Many of those who said they would not be willing to pay to upgrade WWTPs stated that they felt the pharmaceutical industry should pay for the upgrades instead. Others simply felt their taxes were too high already. Some respondents stated that the city should pay, apparently not making the link between the city paying and an increase in municipal taxes. One respondent acknowledged that it was illogical to expect the city to pay for upgrades to WWTPs while refusing to pay her share in taxes, but said that, nevertheless, this was how she felt. The difference between the responses in the attitudinal questions and the willingness to pay question likely reflects differences between the ideal and the real. Respondents know they should protect the environment, but when faced with the real possibility of funding management action out of their own pockets/through their taxes, are much less willing to support management action. Even the willingness to pay question may overestimate respondents' true willingness to contribute financially to the management of PhACs in the environment, as respondents are more likely to object when actually sent a bill, than when asked theoretically, with no obligation to pay, how much they would be willing to contribute (Kontogianni, Langford, Papandreou, & Skourtos, 2003). The mixed response regarding
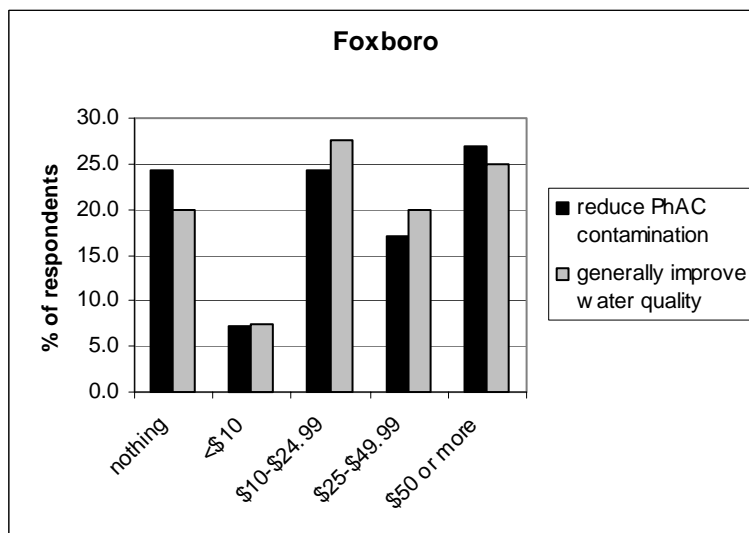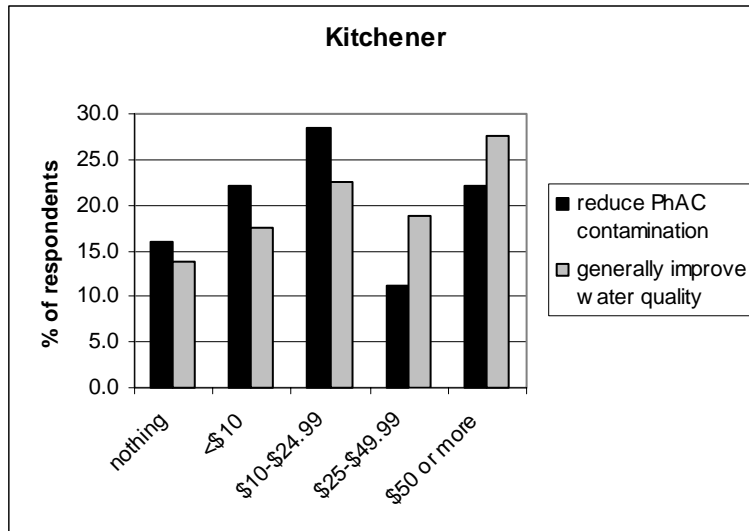
Figure 4.27. Willingness to pay to upgrade wastewater treatment to reduce water contamination by pharmaceuticals (PhACs), and to generally improve water quality, among survey respondents. Respondents were asked how much they would be willing to pay per year to achieve these two objectives.

willingness to pay for upgrades to WWTPs, even knowing that such an upgrade could improve water quality in general, suggests that the Region of Waterloo would likely face protests from residents if expensive wastewater treatment technologies were installed and resulted in an increase in taxes.

4.5.3 Expense of upgrading WWTPs

While residents would likely protest the installation of expensive wastewater treatment technology, not all effective advanced treatment options are highly expensive. Ozonation can effectively remove PhACs from water/wastewater (Huber, Canonica, Park, & Von Gunten, 2003; Ternes et al., 2003), especially when DOC concentrations are not excessively high (Zwiener & Frimmel, 2000). While there is some concern about ozonation byproducts, Ternes et al. (2003) suggest that such byproducts are unlikely to be pharmacologically active. They estimate that the cost of installing and operating ozonation at a large-scale treatment plant would be no more than 0.05 Euros/m^3 of wastewater ($ 0.073 CDN/m^3). The Kitchener wastewater treatment plant treats 60 000 m^3/day. The yearly cost of upgrading the Kitchener WWTP to include ozonation, per resident of Kitchener, would therefore be:

(0.073 $/$m^3$ x 60 000 m^3/d x 365 d/yr)/180 000 residents = $ 8.9/yr per resident

While one must be cautious in extrapolating the results of the Kitchener survey to the population as a whole, given that the survey was not random, it is of interest that 62% of Kitchener respondents said they would be willing to pay $10 or more to upgrade the local WWTP to better remove PhACs, and 68% said they would pay $10 or more to generally improve water quality. This suggests that many Kitchener residents would find the cost of installing an ozonation system in the WWTP acceptable. The Region should therefore consider adding ozonation to the Kitchener WWTP as a future management strategy to mitigate the environmental impacts of PhACs. However it should also take into account the energy-intensive nature of ozonation, which uses 40-50% more energy than a regular, secondary WWTP (Larsen, Lienert, Joss, & Siegrist, 2004), and the generation of ozonation by-products (McDowell, Huber, Wagner, Von Gunten, & Ternes, 2005).

Membrane filtration, while effectively removing PhACs from water (Heberer, Feldmann, Reddersen, Altmann, & Zimmerman, 2002) appears to be somewhat less feasible as a treatment option, as it is both more expensive and more energy-intensive than ozonation (Larsen et al., 2004). Côté, Masini and Mourato (2004) estimate that the total lifecyle cost of treating sewage wastewater to a quality suitable for irrigation reuse with an integrated membrane bioreactor (MBR) would be $0.20/$m^3$ for a large plant such as the Kitchener WWTP. Assuming this cost is in U.S. dollars, the cost in Canadian

dollars would be $0.24/m^3, and the cost per resident of installing such as system at the Kitchener WWTP would be:

(0.24 $/m^3 x 60 000 m^3/d x 365 d/yr)/180 000 residents = $ 29/yr per resident

Only 33% of respondents in the Kitchener survey were willing to pay more than $25 per year to reduce water contamination by pharmaceuticals, although 46% were willing to pay the same amount to generally improve water quality. Nevertheless membrane filtration should not be entirely ruled out as a future treatment method to remove PhACs from wastewater, as it has one significant advantage over ozone: it does not generate any reaction products.

4.5. Conclusions: Implications for management

The results of the analyses of WWTP influent and effluent and the social surveys have several implications for management. The concentrations of PhACs in the WWTP effluents are comparable with those found in international studies, although PhAC concentrations leaving the Foxboro plant are elevated. Antibiotic concentrations are particularly high in Foxboro and sulfamethoxazole concentrations are surprisingly high in Kitchener, although they may be outliers rather than typical values. PhAC concentrations in Foxboro effluent are generally higher than in Kitchener but environmental contamination by Foxboro wastewater will also be more localized, as the wastewater is released to the subsurface through a septic tile bed. Although a groundwater well is located near the Foxboro WWTP, the presence of a thick aquitard means that the contamination of the underlying aquifer and therefore the production well, is unlikely (pers. comm.., D. Andrews, manager of wastewater operations, Region of Waterloo, 2005). In Kitchener, PhAC concentrations in effluent are lower, but wastewater is discharged to the Grand River, making PhACs from the Kitchener plant more likely to impact aquatic ecosystems locally or downstream. Furthermore, the environmental loading of pharmaceuticals is higher in Kitchener. Taking a precautionary approach to the protection of groundwater and the quality of the Grand River, given that PhAC concentrations in the Kitchener and Foxboro effluents are similar – and for some PhACs, higher – than those found in other urban areas, it is reasonable to consider management action to reduce the loading of PhACs to the environment in the Region of Waterloo.

The results of the survey suggest that residents are interested in managing an environmental problems such as water contamination by PhACs, as they are concerned about water contaminants, even if their effects are unclear and even if the contaminants are not likely a threat to human health. However, many residents would not support expensive management strategies. Ozonation is a technology which effectively removes PhACs from water and wastewater (Huber et al., 2003; Ternes et al., 2003; Zwiener & Frimmel, 2000), yet is not overly expensive, at an estimated cost of $ 8.9 per year per for Kitchener residents. It therefore represents a viable management option which the Region of Waterloo might install to mitigate the release of PhACs from the Kitchener WWTP, although the additional 40-50% energy requirements for ozonation and the generation of by-products, must also be considered (Larsen et al., 2004; McDowell et al., 2005). In Foxboro, a general lack of effectiveness in plant operations may require an upgrade in the near future. Such a general upgrade may help to improve the removal of PhACs at the plant, without resorting to expensive or energy-intensive technologies. Furthermore, optimization of plant parameters, such as sludge retention time (SRT), may represent a means of improving PhAC removal at both Foxboro and Kitchener WWTPs without the expense of high-tech upgrades (Clara et al., 2005; Metcalfe, Koenig et al., 2003).

Disposal of unused and expired medications is another aspect of environmental PhAC loading which could be addressed relatively inexpensively. Furthermore, this flexible management strategy meets the requirements of adaptive planning (Holling, 1978; Lessard, 1998) (see Ch. 3), as it is easier to modify than technological strategies such as advanced wastewater treatment. Many residents of Kitchener and Foxboro dispose of medications in the toilet or garbage, which contributes to the environmental loading of PhACs. Many of the residents are not aware of the possibility of returning their unused or expired medications to the pharmacy or to household hazardous waste day, nor are they aware of the environmental reasons for doing so. Those residents who are informed of the possibility of returning unused/expired medications to the pharmacy are more likely to do so. Return rates for unused/expired drugs are approximately 25 % higher among residents aware that they can return unused/expired drugs to the pharmacy, than among general survey respondents (Fig. 4.21). Clearly, education is essential to

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improve the pharmaceutical disposal habits of local residents. Education programs need not be expensive; instead, the Region of Waterloo may want to collaborate with pharmacies to make residents aware of the possibility of and need for proper disposal. In Europe, the pharmaceutical industry is often involved in pharmaceutical returns programs (Greiner & Rönnefahrt, 2003; SIGRE, 2002). This is also the case in British Columbia (Government of British Columbia, 1997).   Education programs could be as simple as handing out pamphlets on pharmaceutical disposal to all respondents who purchase behind the counter medications, or verbally mentioning disposal as a part of counselling by the pharmacist. Educating local residents about the need to protect the environment through proper disposal of pharmaceuticals may have several added benefits. It may increase the awareness among residents that their individual actions, such as waste disposal, have an environmental impact. This may increase their environmental consciousness in general, and may lead to a greater sense of responsibility towards the environment – a sense of environmental stewardship. If residents are taught that all of their actions have environmental relevance, and that all products require proper disposal – whether recycling, composting, or special returns programs – environmental considerations may begin to play a greater role in their general behaviour.

4.6. References

Arnstein, S. R. (1969). A ladder of citizen participation. *American Institute of Planners Journal*(July), 216-224.

Baronti, C., Curini, R., D'Ascenzo, G., Di Corcia, A., Gentili, A., & Samperi, R. (2000). Monitoring natural and synthetic estrogens at activated sludge sewage treatment plants and in a receiving river water. *Environmental Science and Technology, 34*(24), 5059-5066.

Beierle, T. C., & Konisky, D. M. (2001). What are we gaining from stakeholder involvement? Observations from environmental planning in the Great Lakes. *Environment and Planning C: Government and Policy, 19*, 515-527.

Bound, J. P., Kitsou, K., & Voulvoulis, N. (2006). Household disposal of pharmaceuticals and perception of risk to the environment. *Environmental Toxicology and Pharmacology, 21*, 301-307.

Bound, J. P., & Voulvoulis, N. (2004). Pharmaceuticals in the aquatic environment -- a comparison of risk assessment strategies. *Chemosphere, 56*, 1143-1155.

Briassoulis, H. (1989). Theoretical orientations in environmental planning: an inquiry into alternative approaches. *Environmental Management, 13*(4), 381-392.

Bridges, O., Bridges, J., & Potter, J. F. (2000). A generic comparison of the airborne risks to human health from landfill and incinerator disposal of municipal solid waste. *The Environmentalist, 20*, 325-334.

Brooks, B. W., Foran, C. M., Richards, S. M., Weston, J., Turner, P. K., Stanley, J. K., et al. (2003). Aquatic ecotoxicology of fluoxetine. *Toxicology Letters, 142*, 169-183.

Brooymans, H. (2005, Tuesday October 25). Alberta rivers a pharmaceutical soup: Could render antibiotics useless, feminize fish in long run. *The Edmonton Journal,* p. A3.

Bund/Länderausschuss für Chemikaliensicherheit (BLAC). (2003). *Arzneimittel in der Umwelt: Auswertung der Untersuchungsergebnisse*. Hamburg: 61st Umweltministerkonferenz.

Cameron, J. (2001). The precautionary principle in international law. In A. Jordan (Ed.), *Reinterpreting the precautionary principle* (pp. 113-142). London: Cameron May.

Canadian Centre for Pollution Prevention. (2005). *Regional Municipality of Waterloo*. Retrieved June 27, 2005, from http://www.c2p2online.com/print.php3?section=44&doc_id=318&session=

Canadian Standards Association. (1997). *CAN/CSA-Q850-97: Risk management: a guideline for decision-makers*. Etobicoke, ON.

Carballa, M., Omil, F., Lema, J. M., Llompart, M., García-Jares, C., Rodríguez, I., et al. (2004). Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. *Water Research, 38*, 2918-2926.

CEPA. (1999). Canadian Environmental Protection Act: The House of Commons of Canada, Bill C-32, as passed by the House of Commons, June 1, 1999.

Clara, M., Kreuzinger, N., Strenn, B., Gans, O., & Kroiss, H. (2005). The solids retention time -- a suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants. *Water Research, 39*, 97-106.

Commission of the European Communities. (2000). *Communication from the Commission on the precautionary principle* (No. COM (2000)1). Brussels.

COMPAS for Health Canada. (2002, November 6). *F&DA environmental assessment regulations project benchmark survey: a report to Health Canada (POR-02-13) Office of Regulatory and International Affairs*. Retrieved February 25, 2004, from http://www.hc-sc.gc.ca/ear-ree/fda_report_entire_e.html#executive

Côté, P., Masini, M., & Mourato, D. (2004). Comparison of membrane options for water reuse and reclamation. *Desalination, 167*, 1-11.

CPMP. (2001). *Discussion paper on environmental risk assessment of non-genetically modified organisms (non-GMO) containing medicinal products for human use.* (No. CPMP/SWP/4447/00). London, UK: Committee for Proprietary Medicinal Products.

Dyck, W., Del Bel Belluz, D., & Craig, L. (1999). *Current directions in environmental risk assessment and management*. Waterloo, ON: Network for Environmental Risk Assessment and Management.

Fong, P. P. (1998). Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. *Biology Bulletin, 194*, 143-149.

Fong, P. P. (2001). Antidepressants in aquatic organisms: a wide range of effects. In C. G. Daughton & T. L. Jones-Lepp (Eds.), *Pharmaceuticals and personal care products in the environment: scientific and regulatory issues* (pp. 264-281). Washington, D.C.: American Chemical Society.

Friedmann, J. (1987). *Planning in the public domain: from knowledge to action*. Princeton, NJ: Princeton University Press.

Golet, E. M., Alder, A. C., & Giger, W. (2002). Environmental exposure and risk assessment of fluoroquinolone antibacterial agents in wastewater and river water of the Glatt Valley watershed, Switzerland. *Environmental Science and Technology, 36*(17), 3645-3651.

Golet, E. M., Xifra, I., Siegrist, H., Alder, A. C., & Giger, W. (2003). Environmental exposure assessment of fluoroquinolone antibacterial agents from sewage to soil. *Environmental Science and Technology, 37*(15), 3243.

Goñi-Urriza, M., Capdepuy, M., Arpin, C., Raymond, N., Caumette, P., & Quentin, C. (2000). Impact of urban effluent on antibiotic resistance of riverine *Enterobacteriaceae* and *Aeromonas* spp. *Applied and Environmental Microbiology, 66*(1), 125-132.

Government of British Columbia. (1997). *Waste management act: Post-consumer residual stewardship program regulation. B.C. Reg. 111/97, O.C. 333/97.*

Government of Canada. (2001). *A Canadian perspective on the precautionary approach/principle: discussion document*. Retrieved May 10, 2004, from http://www.ec.gc.ca/econom/discussion_e.htm

Grand River Conservation Authority. (2001). *The Grand River Watershed*. Retrieved July 6, 2005, from http://www.grandriver.ca/index/document.cfm?Sec=12&Sub1=55&sub2=24

Grand River Conservation Authority (2007). GRCA monitoring network: river conditions summary. Retrieved March 12, 2007 from http://www.grandriver.ca/index/document.cfm?sec=2&sub1=10&sub2=0.

Greiner, P., & Rönnefahrt, I. (2003, April 14-16). *Management of environmental risks in the life cycle of pharmaceuticals*. Paper presented at the Envirapharma, Lyon.

Guardabassi, L., Petersen, A., Olsen, J. E., & Dalsgaard, A. (1998). Antibiotic resistance in acinetobacter spp. isolated from sewers receiving waste effluent from a hospital and a pharmaceutical plant. *Applied and Environmental Microbiology, 64*(9), 3499-3502.

Hartmann, A., Alder, A. C., Koller, T., & Widmer, R. M. (1998). Identification of fluoroquinolone antibiotics as the main source of *umuC* genotoxicity in native hospital wastewater. *Environmental Toxicology and Chemistry, 17*(3), 377-382.

Heberer, T. (2002a). Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicology Letters, 131*, 5-17.

Heberer, T. (2002b). Tracking persistent pharmaceutical residues from municipal sewage to drinking water. *Journal of Hydrology, 266*, 175-189.

Heberer, T., Feldmann, D., Reddersen, K., Altmann, H., & Zimmerman, T. (2002). Production of drinking water from highly contaminated surface waters: Removal of organic, inorganic, and microbial contaminants applying mobile membrane filtration units. *Acta hydrochimica hydrobiologia, 30*, 24-33.

Heberer, T., Schmidt-Bäumier, K., & Stan, H. J. (1998). Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part 1: Drug residues and other polar contaminants in Berlin surface and groundwater. *Acta Hydrochimica Hydrobiologia, 26*(5), 272-278.

Hirsch, R., Ternes, T., Haberer, K., & Kratz, K.-L. (1999). Occurrence of antibiotics in the aquatic environment. *The Science of the Total Environment, 225*, 109-118.

Holling, C. S. (1978). *Adaptive environmental assessment and management*. Chichester: John Wiley & Sons.

Huber, M. M., Canonica, S., Park, G.-Y., & Von Gunten, U. (2003). Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environmental Science and Technology, 37*(5), 2003.

Jobling, S., Nolan, M., Tyler, C. R., Brightly, G., & Sumpter, J. P. (1998). Widespread sexual disruption in wild fish. *Environmental Science and Technology, 32*, 2498-2506.

Jorgensen, S. E., & Halling-Sorensen, B. (2000). Drugs in the environment. *Chemosphere, 40*, 691-699.

Khan, S. J., & Ongerth, J. E. (2004). Modeling of pharmaceutical residues in Australian sewage by quantities of use and fugacity calculations. *Chemosphere, 54*, 355-367.

Kiffmeyer, T., Türk, J., Schmidt, K., Becker, B., Kabasei, S., Kuss, H.-M., et al. (2003, April 14-16). *Minimisation of human drug input by oxidative treatment of toilet effluents from hospital wards.* Paper presented at the Envirpharma Conference, Lyon.

Kontogianni, A., Langford, I. H., Papandreou, A., & Skourtos, M. S. (2003). Social preferences for improving water quality: an economic analysis of benefits from wastewater treatment. *Water Resources Management, 17*, 317-336.

Kümmerer, K., Al-Ahmad, A., & Mersch-Sundermann, V. (2000). Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test. *Chemosphere, 40*, 701-710.

Kümmerer, K., & Henninger, A. (2003). Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clinical Microbiology and Infection, 9*, 1203-1214.

Kuspis, D. A., & Krenzelok, E. P. (1996). What happens to expired medications? *Veterinary and human toxicology, 38*, 48-49.

Länge, R., & Dietrich, D. (2002). Environmental risk assessment of pharmaceutical drug substances -- conceptual considerations. *Toxicology Letters, 131*, 97-104.

Larsen, T. A., Lienert, J., Joss, A., & Siegrist, H. (2004). How to avoid pharmaceuticals in the aquatic environment. *Journal of Biotechnology, 113*, 295-304.

Larsson, D. G. J., Adolfsson-Erici, M., Parkkonen, J., Pettersson, M., Berg, A. H., Olsson, P.-E., et al. (1999). Ethinyloestradiol -- an undesired fish contraceptive? *Aquatic Toxicology, 45*, 91-97.

Lee, H.-B., Sarafin, K., Peart, T. E., & Svoboda, M. L. (2004). Acidic pharmaceuticals in sewage -- methodology, stability test, occurrence, and removal from Ontario samples. *Water Quality Research Journal of Canada, 38*(4), 667-682.

Lessard, G. (1998). An adaptive approach to planning and decision-making. *Landscape and Urban Planning, 40*, 81-87.

Lindberg, R. H., Olofsson, U., Rendahl, P., Johansson, M. I., Ysklind, m., & Andersson, B. A. V. (2006). Behavior of fluoroquinolones and trimethoprim during mechanical, chemical, and active sludge treatment of sewage water and digestion of sludge. *Environmental Science and Technology, 40*(3), 1042-1048.

Lishman, L., Smyth, S. A., Sarafin, K., Kleywegt, S., Toito, J., Peart, T., et al. (2006). Occurrence and reduction of pharmaceuticals and personal care products by municipal wastewater treatment plants in Ontario, Canada. *Science of the Total Environment, 367*, 544-558.

McDaniels, T., Gregory, R., & Fields, D. (1999). Democratizing risk management: successful public involvement in local water management decisions. *Risk Analysis, 19*(3), 497-510.

McDowell, D., Huber, M. M., Wagner, M., Von Gunten, U., & Ternes, T. A. (2005). Ozonation of carbamazepine in drinking water: identification and kinetic study of major oxidation products. *Environmental Science and Technology, 39*, 8014-8022.

Metcalfe, C. D., Koenig, B. G., Bennie, D. T., Servos, M., Ternes, T. A., & Hirsch, R. (2003). Occurrence of neutral and acidic drugs in the effluents of Canadian sewage treatment plants. *Environmental Toxicology and Chemistry, 22*(12), 2872-2880.

Metcalfe, C. D., Miao, X.-S., Koenig, B., & Struger, J. (2003). Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada. *Environmental Toxicology and Chemistry, 22*(12), 2881-2889.

Miao, X.-S., Bishay, F., Chen, M., & Metcalfe, C. D. (2004). Occurrence of antimicrobials in the final effluents of wastewater treatment plants in Canada. *Environmental Science and Technology, 38*, 3533-3541.

Ministry of the Environment. (2001). *Certificate of approval municipal and private sewage works number 8520-4X8RRT*.

Mittelstaedt, M. (2003). Drug traces found in cities' water. *The Globe and Mail, February 10,* p. 1.

O'Brien, E., & Dietrich, D. R. (2004). Hindsight rather than foresight: reality versus the EU draft guideline on pharmaceuticals in the environment. *TRENDS in Biotechnology, 22*(7), 326-330.

Pascoe, D., Karntanut, W., & Müller, C. T. (2003). Do pharmaceuticals affect freshwater invertebrates? A study with the cnidarian *Hydra vulgaris*. *Chemosphere, 51*(521-528).

Petts, J. (1994). Effective waste management: understanding and dealing with public concerns. *Waste Management & Research, 12*, 207-222.

Porteous, A. (2001). Energy from waste incineration -- a state of the art emissions review with an emphasis on public acceptability. *Applied Energy, 70*, 157-167.

Purdom, C. E., Hardiman, P. A., Bye, V. J., Eno, N. C., Tyler, C. R., & Sumpter, J. R. (1994). Estrogenic effects of effluents from sewage treatment works. *Chemical Ecology, 8*, 275-285.

Reddersen, K., Heberer, T., & Dünnbier, U. (2002). Identification and significance of phenazone drugs and their metabolites in ground- and drinking water. *Chemosphere, 49*, 539-544.

Region of Waterloo. (2002). *Region of Waterloo wins FCM-CH2M Hill sustainable community award*. Retrieved June 27, 2005

Region of Waterloo. (2003). *Operations manual (draft): Kitchener wastewater treatment plant*.

Region of Waterloo. (2005). *About the region*. Retrieved June 27, 2005, from http://www.region.waterloo.on.ca/web/region.nsf/DocID/D288A5D8FD4E92A48 5256AF700553211?OpenDocument

Sanderson, H., Johnson, D. J., Reitsma, T., Brain, R. A., Wilson, C. J., & Solomon, K. R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology, 39*, 158-183.

Sanderson, H., Johnson, D. J., Wilson, C. J., Brain, R. A., & Solomon, K. R. (2003). Probabilistic hazards assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids and algae by ECOSARS screening. *Toxicology Letters, 144*(3), 383-395.

Seiler, J. (2002). Pharmacodynamic activity of drugs and ecotoxicology -- can the two be connected? *Toxicology Letters, 131*, 105-115.

SIGRE. (2002). *Por la salud de la naturaleza: Memoria de actividades* (Pamphlet).

Stevenson, M. (2003). *Pharmaceuticals found in four cities' tap water*. Retrieved August 5, 2005, from http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/1044053088271_394622 88/?hub=SciTech

Stumpf, M., Ternes, T. A., Wilken, R.-D., Rodrigues, S. V., & Baumann, W. (1999). Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. *The Science of the Total Environment, 225*, 135-141.

Ternes, T. A. (1998). Occurrence of drugs in German sewage treatment plants and rivers. *Water Research, 32*(11), 3245-3260.

Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M., et al. (2003). Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Research, 37*, 1976-1982.

United Nations General Assembly. (1992). *Report of the United Nations conference on environment and development* (No. A/CONF.151/26 Vol. I). Rio de Janeiro.

Vieno, N. M., Tuhkanen, T., & Kronberg, L. (2005). Seasonal variation in the occurrence of pharmaceuticals in effluents from a sewage treatment plant and in the recipient water. *Environmental Science and Technology, 39*(21), 8220-8226.

Wennmalm, Å. (2003, April 14-16). *Management of pharmaceutical drug residues from public health care in Stockholm County Council*. Paper presented at the Envirpharma Conference, Lyon.

Wilson, B. A., Smith, V. H., Denoyelles, F. J., & Larive, C. K. (2003). Effects of three pharmaceutical and personal care products on natural freshwater algal assemblages. *Environmental Science and Technology, 37*, 1713-1719.

Zwiener, C., & Frimmel, F. H. (2000). Oxidative treatment of pharmaceuticals in water. *Water Research, 34*, 1881-1885.

Chapter 5: Consultation with stakeholders from academic, public, and industrial sectors

Journal Publications based on Ch. 5:

Doerr-MacEwen, N. A., & Haight, M. E. (2006). Expert stakeholders' views on the management of human pharmaceuticals in the environment. *Environmental Management, 38*, 853-866.

Doerr-MacEwen, N. A., & Haight, M. E. Pharmaceuticals in the environment and the precautionary principle: addressing stakeholder concerns. Submitted to the *International Journal of Sustainable Development and Planning* in 2006.

5.1. Introduction

Consultation with stakeholders is an essential component of risk management (Canadian Standards Association, 1997; McColl, Hicks, Craig, & Shortreed, 2000; The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). Stakeholders can be defined as "Any individual, group, or organization able to affect, be affected by, or believe it might be affected by, a decision or activity. The decision-maker(s) is a stakeholder." (Canadian Standards Association, 1997). This chapter presents the results of consultation with international stakeholders from academia, governments and the pharmaceutical industry, through structured interviews. These stakeholders have expertise in the science and management of pharmaceuticals in the environment. The interviews therefore focused largely on eliciting the interviewees' expert opinions regarding the nature of the problem of pharmaceuticals in the environment, and potential management strategies, especially those being used in their respective countries. Expert elicitations are often used to obtain assessments of environmental problems beyond the understanding that can be gleaned from peer-reviewed literature (Morgan, Pitelka, & Shevliakova, 2001; von Krauss, Casman, &

Small, 2004). Interviewees from the government and industrial sectors were also asked to provide insight into the perspectives of their organizations and sectors on the issue of pharmaceuticals in the environment when possible. Understanding gained through the interviews described in this chapter will be used in the evaluation of management strategies in the subsequent chapter.

5.2. Methods

Structured interviews were conducted with 27 expert stakeholders working for governments, universities, and the pharmaceutical and consulting industry, from Canada, the United States and Europe (Table 5.1) (Doerr-MacEwen & Haight, 2006). Environmental non-governmental organizations (ENGOs) were also contacted, but declined to participate in the interviews, citing a lack of personnel and resources to devote to the study. Interviewees were selected through purposive sampling: based on their contributions to the literature on pharmaceuticals in the environment, participation in conferences on pharmaceuticals (PhACs) in the environment, and on recommendations of professional organizations or colleagues. The interviewees were recruited by e-mail. Interviews were conducted in person when possible (n=18), by telephone (n=5) and e-mail (n=4). Participation rates were highest among potential interviewees within the academic sector (~71%), followed by the public (government) sector (~64%), then representation from the pharmaceutical industry (~18%). Sampling was non-random as the purpose of the interviews was not to generate statistics that could be applied across entire populations of stakeholders, but to gain an in-depth understanding of the views of some stakeholders from different sectors. Interview questions asked of members of the pharmaceutical industry differed somewhat from those asked of other interviewees, as these respondents were in a position to provide insight into the particular perspective of the industry. A mixture of open-ended and close-ended questions were used (Greene, Caracelli, & Graham, 1989), with close-ended questions included rating scales and Likert-style questions (Foddy, 1993; Krosnick & Fabrigar, 1997; Palys, 1997. The purpose of the mixed-methods approach was twofold; some questions were complementary, meant to clarify the results of other questions (Greene et al., 1989). For example, open-ended questions asking interviewees to elaborate or explain their answers

Interviewee	Affiliation	Location	Field of Specialty
1	University	Canada	Environmental Toxicology
2	University	Canada	Ecotoxicology
3	University	Canada	Environmental Toxicology
4	University	Canada	Drinking Water Treatment
5	University	Canada	Ecotoxicology
6	University	Canada	Endocrinology
7	University	United States	Environmental Chemistry
8	University	Europe	Chemical/Environmental Engineering
9	University	Europe	Environmental Chemistry
10	Government	Canada	Microbiology
11	Government	Canada	Wastewater Operations
12	Government	Canada	Veterinary Epidemiology
13	Government	Canada	Environmental Assessment
14	Government	United States	Toxicology & Microbiology
15	Government	United States	Environmental Toxicology & Chemistry
16	Government	United States	Hydrology
17	Government	Europe	Biology
18	Government	Europe	Risk Assessment
19	Government	Europe	Clinical Physiology
20	Government	Europe	Environmental Safety Assessment
21	Government	Europe	Environmental Science/Policy
22	Industry (Phm[1].)	Canada	Environmental Management
23	Industry (Phm[1].)	Canada	Scientific Affairs
24	Industry (Phm[1].)	United States	Safety Assessment
25	Industry (Phm[1].)	Europe	Environmental Risk Assessment
26	Industry (Phm[1].)	Europe	Risk Assessment
27	Industry (Con[2].)	Europe	Ecotoxicology

[1] Pharmaceutical Industry

[2] Consulting industry

Table 5.1 List of interviewees, including sector, geographic location, and area of specialty.

to close-ended questions. However, in general, the purpose of the mixed methodology was simply to expand the breadth of inquiry (Greene et al., 1989), using whichever format seemed most appropriate given the nature of the question; in other words, a pragmatic approach (Datta, 1997; Greene & Caracelli, 1997). The interview questions for the academic and public sector participants and the environmental consulting industry, are provided in Appendix E. Questions asked only of participants from the pharmaceutical industry can be found in Appendix F. All interviewees were asked questions relating to the scope and nature of the problem of pharmaceuticals in the environment and their opinions of risk management strategies.

5.3 Results & Discussion

5.3.1 Scope and Nature of the Problem

In the scientific literature on pharmaceuticals in the environment, the scope and nature of the problem continue to be debated: How much of a concern do PhACs in aquatic environments really represent for ecosystem health? Are they likely to detrimentally affect human health? How do they compare to other surface water and groundwater concerns? The answers provided by the interviewees bring new perspectives, not previously expressed in the academic literature.

5.3.1.1 Concern for Ecosystem and/or Human Health?

When asked if PhACs in aquatic environments represented a concern for ecosystem health, human health, both, or neither, the majority (62%) of interviewees indicated that they felt PhACs were of concern with respect to both human health and ecosystem health (Fig. 5.1) (Doerr-MacEwen & Haight, 2006). The reasons for seeing PhACs in the environment as a human health concern varied. Interviewee 18 commented that PhACs are a human health concern because of their bioactive nature and because they are present in groundwater, drinking water and recreational waters, not just in surface water removed from human use. Interviewee 6 suggested that regardless of whether or not evidence existed that PhACs in aquatic environments might harm human health, action should be taken to protect humans against consumption: "What are these drugs doing in water? i.e. Why don't we improve the treatment of water? Improve the

quality of drinking water in general?" Several interviewees identified factors other than scientific evidence that should be considered when addressing the problem from a policy/management perspective. Interviewee 1 stated, "I believe it is only ecosystem health from a science perspective. But from a public policy perspective, I think it's both [a human health and an ecosystem health concern]". Two interviewees believed a precautionary approach should be taken to the management of the problem, and this meant including human health as an area of concern. Interviewee 10 emphasized the need to take public concerns seriously and not to dismiss perceptions of risk which differ from those of scientific experts: "Impacts on human health will be marginal, but there is human concern and apprehension regarding this issue, which must be considered." These comments underline the importance of normative, value-based considerations in the management of PhACs in the environment.

Several interviewees who did not believe that PhACs were of concern for human health cited low PhAC concentrations in drinking water, together with extensive testing of pharmaceuticals for human safety, as a basis for their opinions. For example, interviewee 25 stated, "No human health concern as all publications so far show a very high margin of safety between measured environmental concentrations and worst-case intake of 2 L of surface water per day." Interviewee 26 explained, "It seems to me that there's a very, very wide margin of safety, that you'd have to take certain drugs every day of your life for 70 years and you'd still have a very wide safety margin."

The potential for effects of PhACs on ecosystems was generally seen as a greater concern than the potential for human health effects; 81% of interviewees believed that pharmaceuticals were an ecosystem health concern. Interviewees cited three main reasons for their view that PhACs were of concern for aquatic ecosystem health: 1) the bioactive nature of pharmaceuticals, 2) continuous exposure of aquatic species to PhACs and 3) early findings in laboratory experiments of effects on aquatic organisms,

(a)

(b)

(c)
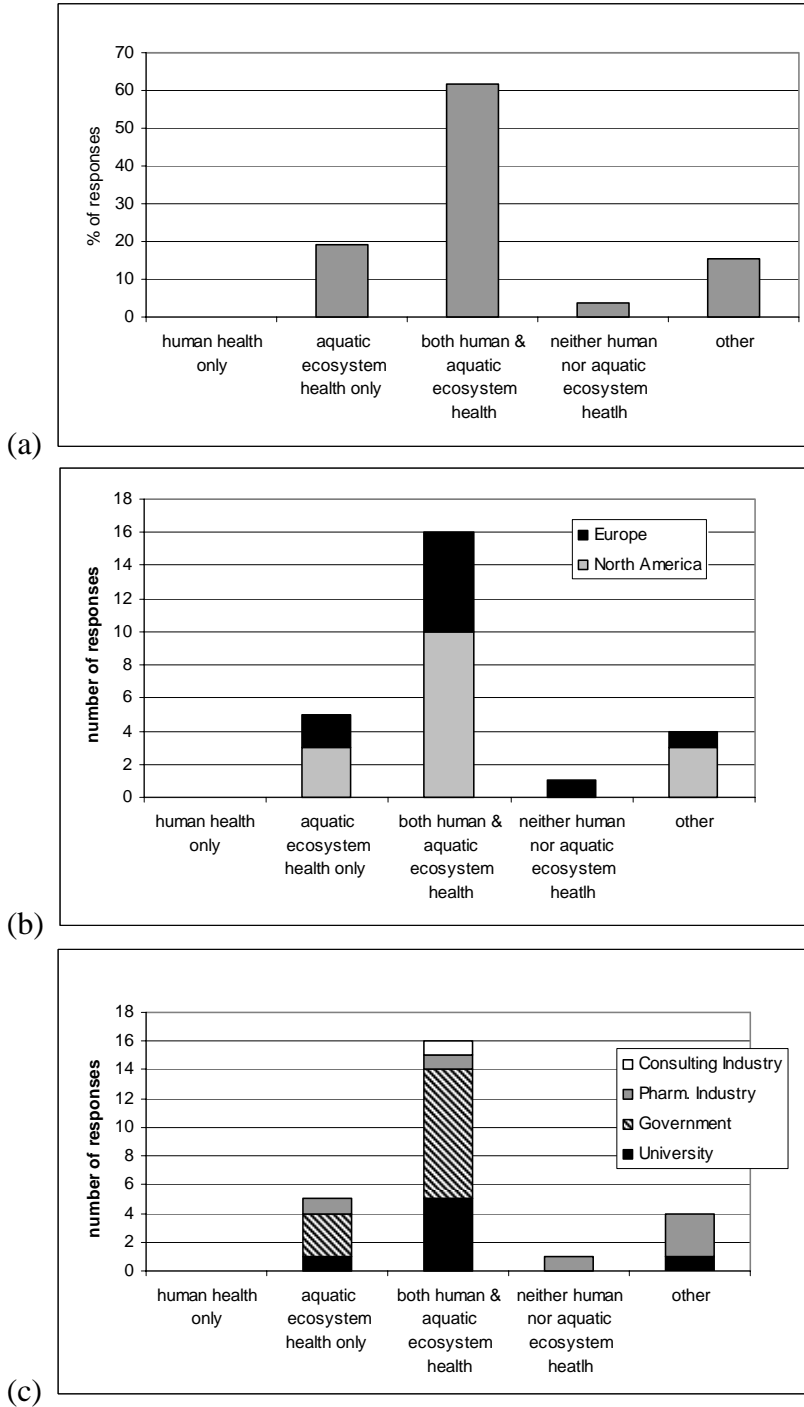
Figure 5.1. Responses of interviewees when asked if pharmaceuticals in surface water and groundwater represented a concern for human health, ecosystem health, both, neither, or other a) percentages of total number of responses, b) number of responses in each category according to geographic location, c) number of responses divided according to sector.

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especially primary organisms. Interviewee 18 explained why ecosystem impacts were of particular concern as follows: "The difference being that for humans, it still would only be periodic, sporadic exposure; for aquatic species, they're going to be swimming in it." Interviewee 12 stated, "It just makes scientific sense that when you're introducing agents as powerful as antimicrobials into the ecosystem, that you're going to be effecting a change." However some interviewees did not believe PhACs were detrimental to aquatic ecosystems, citing a lack of evidence of effects, with the exception of the reasonably well understood localized effects of 17α-ethinylestradiol (Jobling, Nolan, Tyler, Brightly, & Sumpter, 1998; Purdom et al., 1994). For example, Interviewee 26 reasoned, "Let's say we'll make a guess more drugs are used today than were used 20 years ago. The macro analysis actually is the ecosystem doesn't seem to be getting any worse." It is perhaps of note, however, that four of the five respondents who did not believe PhACs were of concern for ecosystems (answering "neither" or "other", shown in Figure 5.1c), were representatives of the pharmaceutical industry. Interviewees from different sectors may tend towards certain perceptions of the issue of pharmaceuticals in the environment, with employees of the pharmaceutical industry possibly having more conservative views than those from the academic (university) and public (government) sectors.

5.3.1.2 *Likelihood and magnitude of effects*

It was of interest to assess the respondents' perception of the likelihood and magnitude of the effects of concern. Because of the complexities of assessing the effects of environmental mixtures of PhACs on aquatic ecosystems and human health (see discussion in Chapter 2), it is impossible at this time to calculate probabilities for such effects. Thus a rough, qualitative assessment of probability of "serious or irreversible damage" was sought. This was completed using bipolar Likert-style questions, two levels of intensity (very and somewhat) towards each pole, and a neutral position in the middle (Appendices E & F)(Krosnick & Fabrigar, 1997). The terms "serious or irreversible damage" were employed as an indication of magnitude of effects, because of their use in the Rio Declaration on Environment and Development (United Nations General Assembly, 1992) and the Canadian Environmental Protection Act (CEPA, 1999), to invoke precautionary management action. The most common response in terms of

ecosystem effects was that PhACs were somewhat likely to induce serious or irreversible damage to aquatic ecosystems (Fig. 5.2a). 61% of interviewees believed PhACs were either very or somewhat likely to cause serious or irreversible damage to aquatic ecosystems. Interestingly, 75% of European interviewees held this view, as compared with 53% of North Americans (Fig. 5.2b). Also of interest are the variations between the responses given by member of different sectors; 83% of interviewees from academia, 60% from government, and none of the interviews from the pharmaceutical industry, thought PhACs would cause serious or irreversible damage to aquatic ecosystems (Fig. 2c). Interviewees who believed serious or irreversible damage to aquatic systems was very or somewhat likely explained this view largely based on known effects, including fish feminization due in part to surface water contamination by 17α-ethinylestradiol, and the death of vultures which had ingested the drug diclofenac through the consumption of dead cattle. Interviewee 18 most clearly expressed this perspective, held by several other interviewees:

> If you think about the impact of diclofenac on the vultures, well you might think this is an irreversible impact on the avian population, because we're already eradicated 95% of the population. That's an extreme example of thing that might happen. Perhaps the same happened somewhere in some nice ecosystem that had some very rare species that we're not aware of, because they're all gone. In risk terms, it's very likely things will happen.

Interviewee 19 discussed the temporal nature of the risks presented by PhACs in the environment, suggesting that a delay in action to mitigate the release of PhACs to the environment would allow for serious and irreversible damage in the future:

> If nobody takes care then it will be very likely that there will be damage. I mean we have started to understand that there is some kind of hazard, for some compounds even a risk, within the past 5-10 years, so it's very new. So if something is done and the input into the environment is reduced, fine. If not, then there will be serious risks.

(a)

(b)

(c)
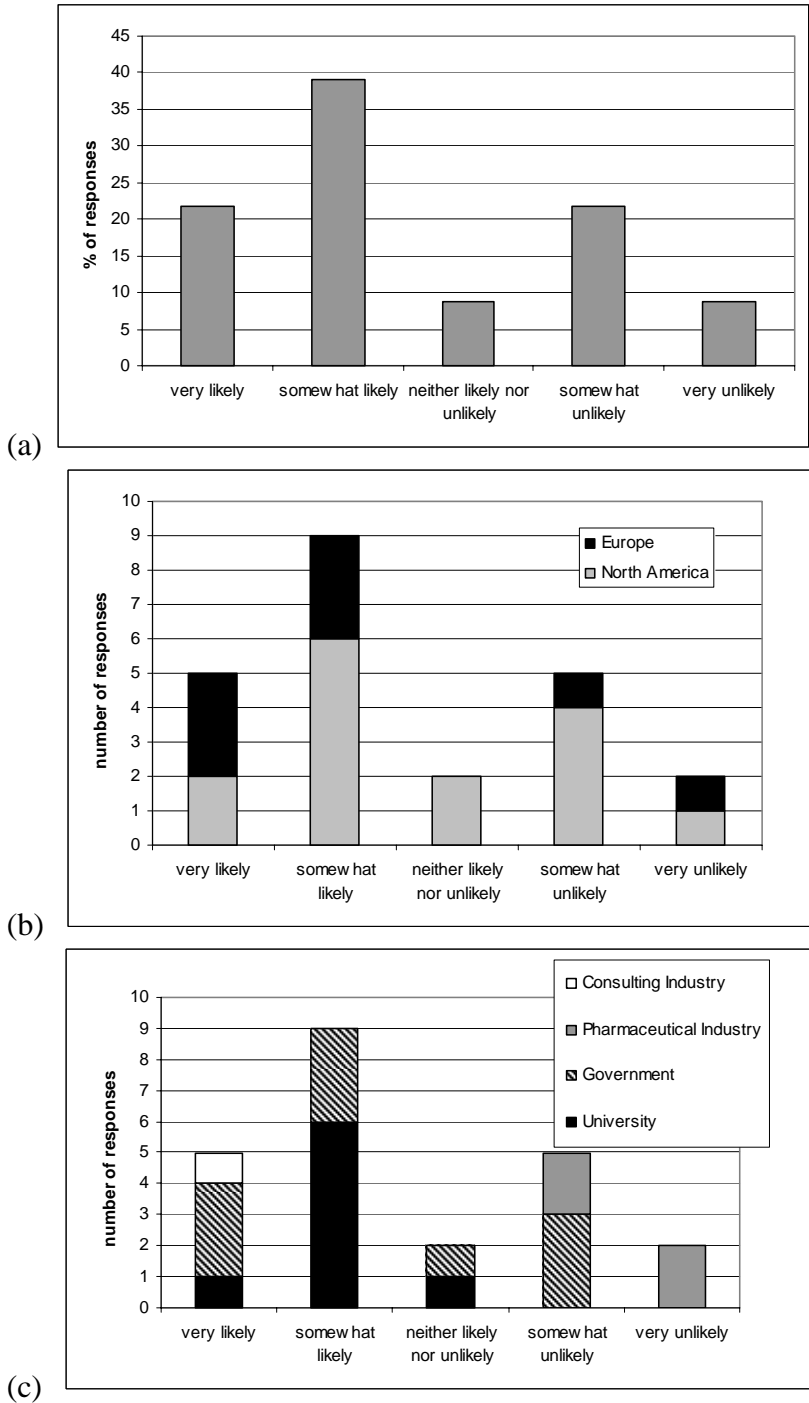
Figure 5.2. Responses of interviewees when asked how likely or unlikely it is that pharmaceuticals in surface water and groundwater will cause serious or irreversible damage to aquatic ecosystems, a) percentages of total number of responses, b) number of responses in each category according to geographic location, c) number of responses divided according to sector.

Interviewees who did not believe serious or irreversible damage to aquatic ecosystems was likely mainly cited the resilience of ecosystems as a reason. They believed that any damage would be reversible; once evidence of damage was found, proper treatment to mitigate environmental contamination could be put in place, and the ecosystem would return to its original state. Interviewee 22 explained:

> If you did have a particular hot spot of pharmaceutical contamination, and if there was a sub-lethal impact, and then you said, O.K., we'll install an appropriate treatment system for that particular locality, I think you would actually get recovery very quickly, because that's what life does.

The interviewees who found serious and irreversible damage unlikely believed in the ecosystem resilience as a characteristic that could be relied upon to avert damage. This was in direct contrast with the view of ecosystems as sensitive, vulnerable, and unknowable/unpredictable, expressed by those interviewees who believed serious and irreversible damage to aquatic ecosystems was likely.

In terms of damage to human health, the responses of interviewees were skewed towards the negative (unlikely to cause serious or irreversible damage), and were less varied than those regarding damage to ecosystems (Fig. 5.3). Only one respondent thought that serious or irreversible damage to human health was at all likely. In the case of human health, 61% of interviewees felt serious or irreversible damage was somewhat or very *un*likely, whereas for aquatic ecosystems, the same number thought it was likely. The reasons for believing serious or irreversible human health damage was unlikely were similar to those the interviewees mentioned when asked if human health was a concern at all. They felt concentrations of PhACs in drinking water were too low to cause such damage. It should be noted, however, that several interviewees who rated serious or irreversible human health damage as "somewhat unlikely", were nevertheless concerned about human health effects; in particular, effects on sensitive sub-populations and humans at sensitive stages of development, such as adolescents, were described. Interviewee 8 expressed a concern that mixtures of environmental contaminants were contributing to decreased sperm counts and increased rates of cancer and allergies, and wondered if pharmaceuticals could be one class of substances, among many, contributing
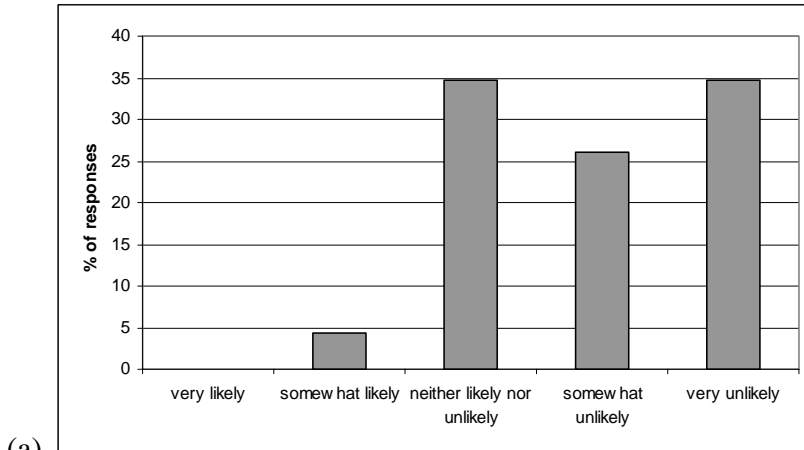
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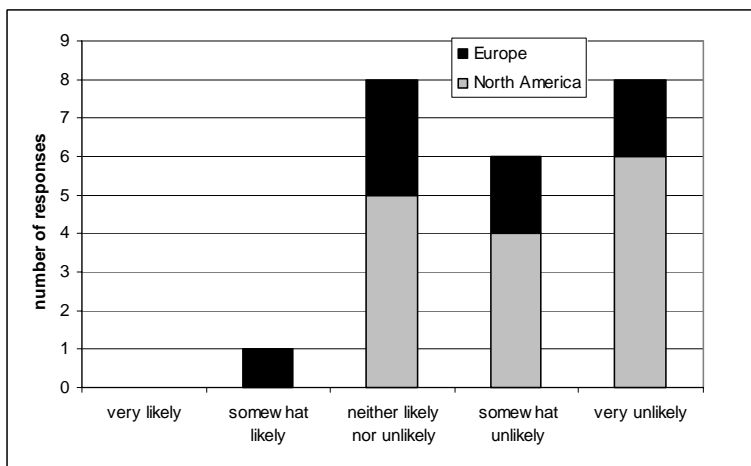
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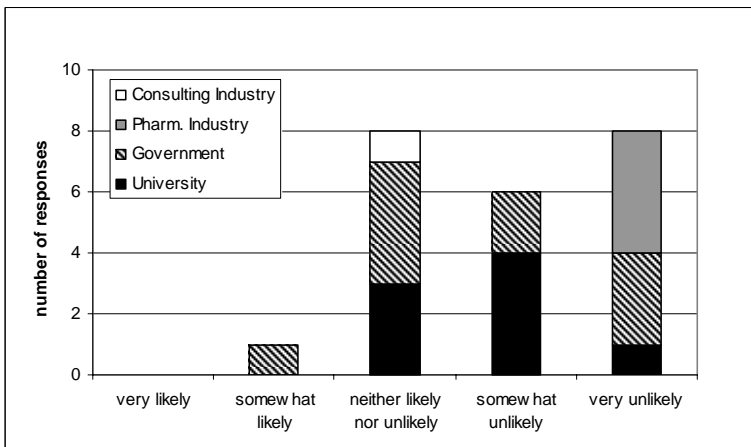
(c)

Figure 5.3. Responses of interviewees when asked how likely or unlikely it is that pharmaceuticals in surface water and groundwater will cause serious or irreversible damage to human health. a) percentages of total number of responses, b) number of responses in each category according to geographic location, c) number of responses divided according to sector.

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to detrimental effects on human health. In other words, while many interviewees did not think human health impacts were likely, several nonetheless believed that the effects of long-term consumption of mixtures of low levels of pharmaceuticals and other substances are not thoroughly understood. Consequently, the possibility of subtle health effects such as endocrine disruption, cannot be ruled out.

5.3.1.3 Ranking of Surface Water and Groundwater Contaminants

As pharmaceuticals represent only one group of water contaminants of concern, and as resources for mitigating environmental contamination are limited, it is of interest to determine how PhACs compare to other contaminants in terms of need for management action. Interviewees from government and academia were asked to rank 7 common surface water and groundwater contaminants in terms of need for management action, in their respective countries (Fig. 5.4). The graphs indicate the frequency with which each contaminant was assigned a ranking by interviewees.   The interviewees gave a very wide range of responses when ranking the need to manage PhACs, compared to their responses for other contaminants like metals and pesticides. Table 5.2 illustrates the overall ranking when the individual rankings by interviewees are aggregated, as well as the aggregated rankings for North America and Europe. PhACs rank 5th out of 7 contaminants in the overall aggregated ranking and the North American ranking, but 4th in the European aggregated rankings (Doerr-MacEwen & Haight, 2006). Several interviewees suggested that chemical contaminants need to be addressed not as separate groups of substances but in terms of the environmental impact of chemical mixtures.

North America	Europe	Total Aggregated
Pathogens	Nutrients	Pathogens
Pesticides	Pesticides	Nutrients
Nutrients	Metals	Pesticides
Metals	*Pharmaceuticals*	Metals
Pharmaceuticals	Pathogens	*Pharmaceuticals*
Organic Solvents	Organic Solvents	Organic Solvents
Road Salt	Road Salt	Road Salt

Table 5.2 Ranking of groundwater and surface water contaminants in order of decreasing need for management action, based on interviewees' aggregatde rankings.

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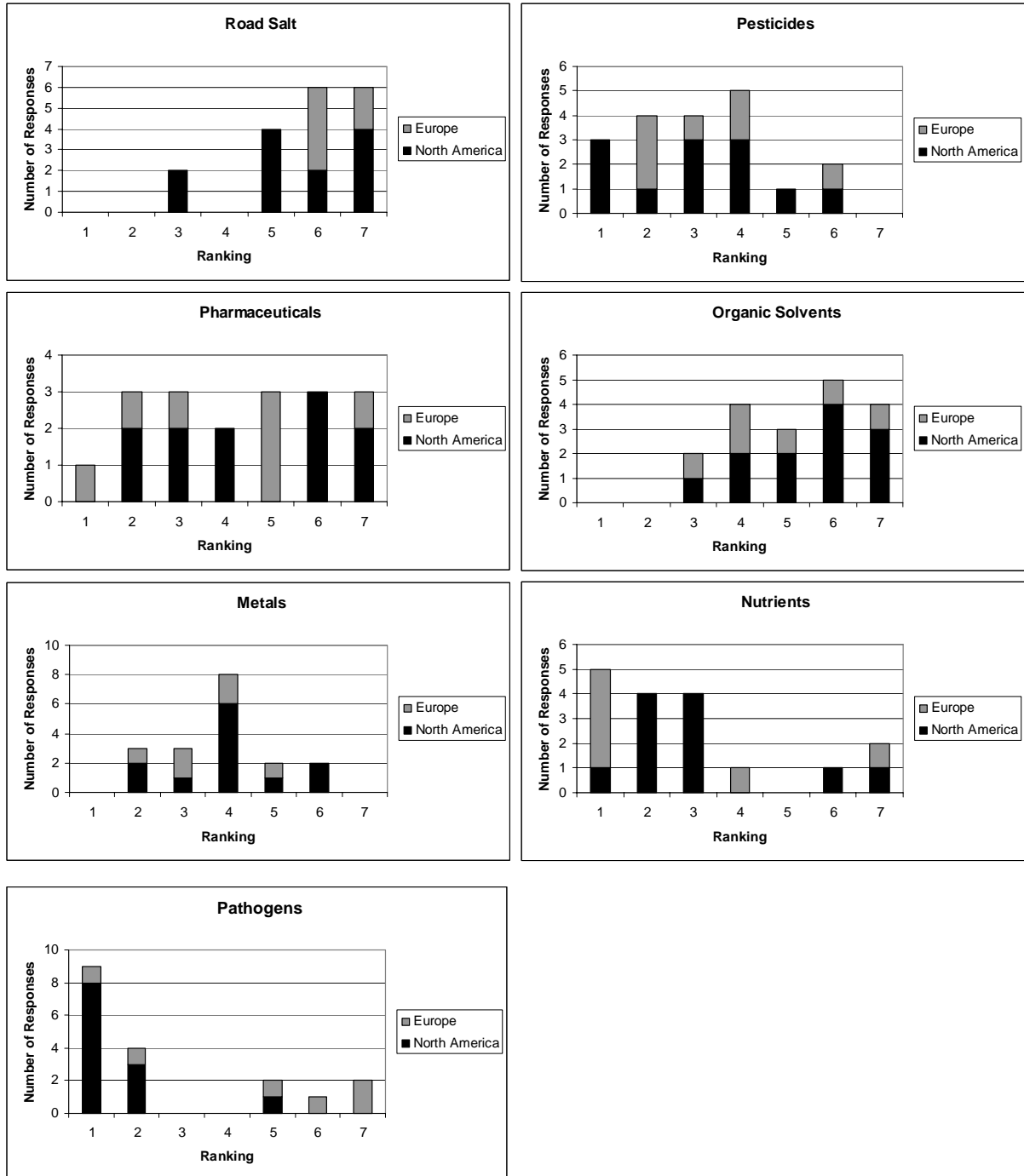
Figure 5.4. Interviewees ranked seven contaminants in order of greatest need for management action, with 1 representing the greatest need for action. These graphs illustrate the frequency with which each contaminant was given each ranking by interviewees.

It is quite striking that pathogens were ranked 1st by North Americans, but 5th – lower than pharmaceuticals – in terms of need for management action, by Europeans. This may be a reflection of different approaches to precaution in Europe and North America. Examples of precautionary action in Wiener and Rogers (2002) suggest that Europeans tend to take a more precautionary stance with respect to chemical contamination and similar issues which present risks to the environment at large. In contrast North Americas tend to have a more precautionary attitude towards human health risks, such as Bovine Spongiform Encephalopathy (BSE) and smoking, which do not necessarily affect ecosystems. PhACs are seen as representing a greater risk to ecosystems than to human health (see Sections 5.3.1 and 5.3.2) whereas contamination of surface water and groundwater by pathogens is of greater concern in terms of human health than ecosystem health (O'Connor, 2002).

5.3.2 Uncertainty

Because of complexities such as mixture effects, the academic literature suggests that a high degree of uncertainty – perhaps ignorance (see Chapter 3, Section 3.2.2.) – exists regarding the effects of PhACs on aquatic ecosystems. The interviewees were asked to score this uncertainty on a scale of 1 to 5, with 1 representing complete certainty (i.e. the ability to calculate risk in probabilistic terms) and 5 representing complete uncertainty (i.e. ignorance). When the scores of the interviewees were aggregated, a score of 3.6 was obtained, indicating a high level of uncertainty, but perhaps not the complete lack of knowledge and understanding occasionally suggested by the literature. All of the interviewees who explained why they had assigned a moderate, rather than a high score in terms of uncertainty, cited known cases of impacts of PhACs on aquatic species. Interviewee 9 explained, "We have cases where we can be quite sure that there is a risk for the environment, for some hormones; that is almost settled," and Interviewee 21 stated, "We are pretty certain drugs are not at levels which are causing acute impacts (death). We have a lot of knowledge about endocrine disrupting effects." Reasons for giving a high score to the level of uncertainty were manifold; Table 5.3 lists the sources of uncertainty mentioned, and the number of interviewees who mentioned each source. The three sources of uncertainty most commonly related were mixture effects, low-level,

chronic effects and a lack of appropriate risk assessment methodology. Clearly these are interrelated, as are many other sources in Table 5.3. Therefore the sources were categorized according to the two main steps in assessing risk to aquatic ecosystems: assessment of exposure and assessment of effects. Sources of uncertainty related to effects were mentioned 21 times, whereas sources related to exposure were only mentioned 5 times. This may reflect the wording of the question, which emphasized effects, or the number of toxicologists participating in the interviews (Table 5.1). However, given that measurements of PhACs in the environment – i.e. of exposure – have been made and published for over a decade (Eckel, Ross, & Isensee, 1993; Stan, Heberer, & Linkerhagner, 1994), Table 5.3 may also reflect a sense that it is mainly a lack of toxicological understanding which constitutes the uncertainty in scientific understanding of the effects of PhACs on aquatic ecosystems.

Source of Uncertainty	Category	Times Mentioned
Mixture effects	Effects	5
Chronic, low-level effects	Effects	4
Appropriate risk assessment methodology	Effects	3
Exposure-effect relationship (dose-response)	Effects/Exposure	2
Effects on low trophic levels: invertebrates, bacteria	Effects	2
Effects on whole ecosystems	Effects	2
Mechanisms of action of PhACs	Effects	2
Understanding of metabolites: presence, effects, etc.	Effects/Exposure	2
Analysis of PhAC concentrations in environmental samples	Exposure	1
Effects assessment: looking at the right endpoints	Effects	1
Exposure pattern	Exposure	1
Fate, persistence	Exposure	1
Bioaccumulation	Effects	1
Metabolism of PhACs within organisms	Effects	1

Table 5.3 Sources of uncertainty in terms of the impacts of PhACs on aquatic ecosystems, as expressed by interviewees, and number of interviewees who mentioned each source.

5.3.3 Research Needs

   The research needs described by the interviewees included many of the areas listed as sources of uncertainty regarding effects of PhACs on aquatic ecosystems, but other research needs were also mentioned. Table 5.4 lists the research needs identified by the interviewees, and the number of interviewees who mentioned each research need. These areas requiring research included a combination of research to better understand exposure, effects and means of mitigating the environmental release of PhACs. It is of interest that, as with the sources of uncertainty, research needs related to assessment of the effects of PhAC were mentioned almost twice as often as research needs related to exposure, and four times as often as research into pollution prevention strategies. This may reflect the makeup of the interviewees, many of whom are toxicologists (Table 5.1). However it may also reflect the state of research into pharmaceuticals in the environment. Research into PhACs began with a focus on detecting PhACs in aquatic and soil environments, but has now progressed into effects assessment, and will, if evidence of effects continues to be found, move into pollution prevention in the future (Fig. 5.5).
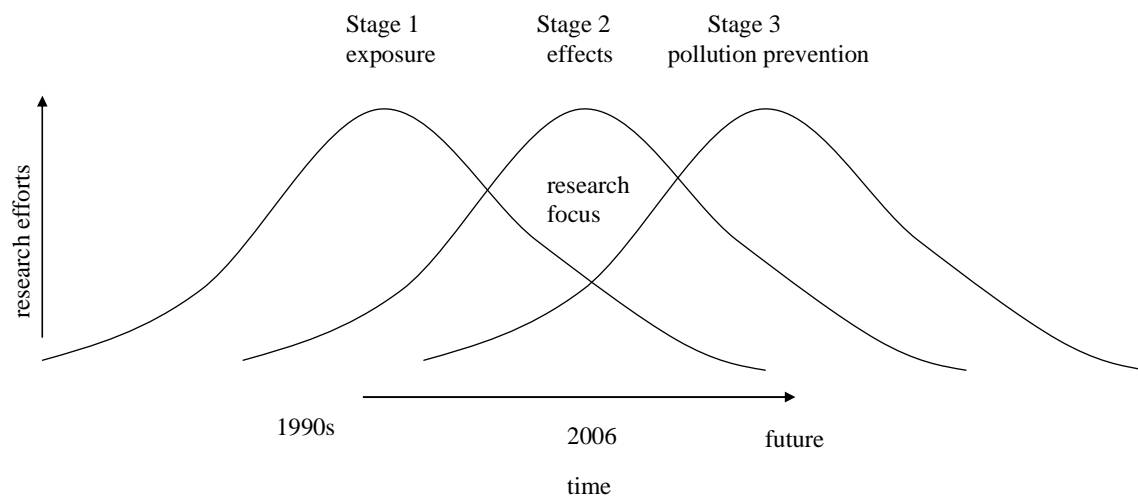
Figure 5.5. Movement of the focus of research on PhACs in the environment from exposure/environmental occurrence, to effects, to pollution prevention.

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Research Need	Category	Times Mentioned
Detection of sub-lethal, chronic effects	Effects	11
Fate, persistence, transport	Exposure	9
Environmental concentrations: exposure	Exposure	5
Systems for testing effects (risk assessment); use of appropriate endpoints	Effects	5
Wastewater and drinking water treatment methods	Pollution prevention	5
Analytical chemistry: methods development	Exposure	4
Ecosystem & population level effects	Effects	4
Mixture effects	Effects	4
Antibiotic resistance	Effects	2
Effects on/interaction with cell membranes	Effects	2
Hormones and endocrine disruption	Effects	2
Reduction of PhAC release at source	Pollution prevention	2
Extrapolation from mammalian toxicity data to ecotoxicity	Effects	1
Human exposure through drinking water	Exposure	1
Human health effects	Effects	1
Localized contamination hot spots: effects?	Exposure/Effects	1
Mechanism of Action	Effects	1
Metabolites	Exposure/Effects	1
Modelling	Exposure/Effects	1
Pharmacodynamic effects	Effects	1
Relative risk, compared to other environmental risks	Exposure/Effects	1

Exposure: 21
Effects: 36
Pollution prevention: 7

Table 5.4 Research needs for the issue of pharmaceuticals in the environment, suggested by interviewees. Research needs are categorized as being related to exposure, effects, and/ or pollution prevention, and the number of interviewees suggesting each research need is shown.

5.3.4 State of Government Activity

5.3.4.1 Research

Government research on PhACs in the environment is, according to the interviewees, more widely distributed throughout the domains of exposure, effects and pollution prevention, than priority research areas suggested by the interviewees (Table 5.5). Governments in Canada, the U.S., and Europe, are conducting extensive environmental monitoring studies for PhACs. Ecotoxicological effects, and water/wastewater treatment methods, are also among the research areas most activity engaged in by governments internationally. Governments need to engage in all of these research areas, as they have a responsibility to collect and publicize data on local occurrences of PhACs in aquatic environments; to contribute to research on effects; and also to explore means of preventing the release of PhACs to aquatic environments.

Research Activity	Category	Times Mentioned
Exposure: environmental monitoring	Exposure	10
Ecotoxicology: effects assessment	Effects	7
Water and wastewater treatment	Mitigation of Release	7
Fate and transport	Exposure/Mitigation of Release	4
Analytical chemistry: methods	Exposure	1
Antibiotic resistance	Effects	1
Ecosystem-wide effects	Effects	1
Hormones & endocrine disruption	Exposure/Effects	1
Mixture effects	Effects	1
Prioritization of PhACs	Effects	1
Sediment: presence of PhACs	Exposure	1

Exposure: 14.5
Effects: 13.5
Pollution prevention: 9

Table 5.5 Research activity engaged in by interviewees' governments, according to interviewees.

5.3.4.2 Management Action

The role of government in management activity to mitigate environmental impacts by PhACs has been minimal, although some countries have made greater strides forward in this area than others. Much of the management activity of governments, as described by the interviewees, is focused on research and environmental risk assessment legislation. This seems to be the case for both European and North American governments, although some European governments seem willing to look beyond risk assessment and research. Interviewee 6 expressed his frustration at the slow pace of the Canadian government in moving from research to management action: "You know, the Canadian way is to study it to death and then realize it's a problem when everybody's been saying it for years." Even in terms of risk assessment legislation, Canada is behind the U.S. and Europe. The U.S. has risk assessment regulations for pharmaceuticals (FDA, 1998); the E.U. has similar regulations for veterinary pharmaceuticals (VICH, 2000), and has draft regulations for human pharmaceuticals (CPMP, 2001). Canada has indicated an interest in developing risk assessment regulations for pharmaceuticals, but progress appears to be hampered by disagreements over whether the regulations should fall under the Canadian Environmental Protection Act or the Food and Drugs Act (Health Canada, 2005). Thus, Canada has not produced any draft risk assessment regulations.

Many of the risk management strategies beyond environmental assessment regulations are incidental to pharmaceuticals, rather than targeted at them. These strategies should not be downplayed, however, as a holistic approach, targeting multiple environmental contaminants, may be the best form of environmental management. According to the interviewees, in Canada, the U.S., and Europe, governments have funded upgrading of wastewater treatment technology; in the E.U., all cities are required to have secondary wastewater treatment as a minimum. Many European countries, including Germany, Switzerland, and the Netherlands, incinerate their municipal solid waste, rather than sending it to landfill. This prevents PhACs from leaching into groundwater, or from ending up in a wastewater treatment plant through landfill leachate collection (pers. comm., D. Andrews, manager of wastewater operations, Region of Waterloo, 2005). Switzerland has enacted regulations to prohibit the spreading of sewage sludge on agricultural land in favour of incineration. This will mitigate contamination of

surface water by PhACs running off from sludge spread on fields, a phenomenon which occurred in the Region of Waterloo (Lissemore, Yang, Hao, et al., 2006). These management activities are often targeted at other contaminants, such as metals, nutrients, and pathogens, but they also reduce environmental contamination by PhACs.

Some of the most forward-looking initiatives for managing pharmaceuticals in the environment have been initiated not by federal governments, but by local governments, and in some cases, the pharmaceutical industry. Stockholm County Council, Sweden, has engaged in a major initiative to classify pharmaceuticals according to criteria relating to their environmental impacts: toxicity, bioaccumulation, and persistence (Stockholm läns landsting, 2005). Pharmaceuticals receive a score from 0 to 3 for each of these criteria, with the total score – the PBT index -- being the sum for the three criteria. A substance with a PBT score of 0 is expected to readily biodegrade, not to bioaccumulate, and to have low ecotoxicity; a PBT score of 9 indicates the reverse. Stockholm County Council publishes this information in the form of "Kloka Listan" ('Wise List') and encourages medical practitioners to select pharmaceuticals with low PBT scores when efficacy, safety, and price are comparable. The council hopes to have the EU adopt their classification system and use it to label medications. In Spain, a pharmaceutical returns program has been set up by an association of pharmaceutical companies, SIGRE, to collect unused and expired medications. Consumers can deposit unused and expired medications in bins at pharmacies. By 2002, 92% of pharmacies in Spain were participants in SIGRE's returns program, and 38 million Spanish citizens participated in the program (SIGRE, 2002). Engagement by multiple levels of government and multiple stakeholders such as in the cases of Stockholm County Council and the SIGRE returns programs, seems to hold much promise for addressing the management of pharmaceuticals in the environment.

5.3.5 Precautionary principle

5.3.5.1 Precautionary management action

Implementing strategies to manage pharmaceuticals in the environment involves taking a precautionary approach (see Ch. 3 for further discussion of the precautionary approach/principle). The goal of such an approach is to act in a timely and proactive way

to prevent environmental degradation, despite uncertainty in scientific understanding of the impacts of PhACs on the environment. The precautionary principle is usually directed towards risk management, not to risk assessment (Commission of the European Communities, 2000; Rogers, 2001). All interviewees, however, including those working only in scientific disciplines, were consulted regarding their views on the precautionary principle and its application to pharmaceuticals in the environment. The interviewees with a predominantly scientific background were included because scientists are, today, expected to participate in management decision-making (Steel, List, Lach, & Shindler, 2004) and because the processes of risk assessment and risk management are more explicitly interlinked today than in the past (McColl et al., 2000; McGarvin, 2001; National Research Council, 1983).

A majority of interviewees supported the use of the precautionary principle, as illustrated in Fig. 5.6a). Sixty-three percent of the interviewees expressed positive opinions towards the principle, including 90% of Europeans, 50% of Canadians, and 40% of American interviewees. When the responses were divided according to sector, 78% of academic (university) interviewees were supportive of the principle, as were 58% of public sector (government) interviewees and 40% of pharmaceutical industry interviewees (Doerr-MacEwen & Haight, 2005). Figures 5.6b) and c) illustrate the number of positive, neutral, and negative responses to the precautionary principle, divided according to location and sector, respectively. Table 5.6 contains examples of statements by interviewees considered to reflect positive, neutral, and negative views of the principle. Several interviewees, including some who supported the use of the precautionary principle in environmental decision making, raised specific concerns about it. These concerns can be categorized into several main theme areas (Table 5.7): Proportionality of the precautionary action, definition of the precautionary principle, socio-economic balance, and level of evidence required to invoke the principle. Risk communication and adaptive planning also emerged as minor themes. Addressing these concerns may increase scientists' comfort with the principle and may minimize the divisive, dichotomous arguments which sometimes erupt over the precautionary principle between scientists and managers/policymakers (Gray & Bewers, 1996; McGarvin, 2001).

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5.3.5.2 Precautionary principle and pharmaceuticals

Tailoring the precautionary principle to manage the distribution of pharmaceuticals in the environment may also help to meet the needs of scientists and managers, while leading to the development of optimal management strategies for PhACs. When asked what the precautionary principle meant for pharmaceuticals in the environment, 16 of the 27 interviewees stated that it meant management action beyond research or the development of risk assessment methodologies and regulations. However many did feel that risk assessment regulations were necessary, although not sufficient, to the application of precaution to PhACs. Seven of the interviewees believed that research entailed precautionary management action. The interviewees who suggested specific management strategies as a result of applying the precautionary principle to PhACs in the environment, favored, in particular, enhancement of sewage treatment technology; reduction of pharmaceutical over-use; development of 'green' (i.e. biodegradable, less toxic) pharmaceuticals; and environmental labeling of pharmaceuticals, although other management strategies were also suggested. Two interviewees were concerned about possible negative implications: increased costs and difficulties in developing and marketing pharmaceuticals, and an artificial goal of zero concentration being set for pharmaceuticals in water. Policy makers may want to consider the positive implications of the principle for the management of PhACs, suggested by the interviewees, and avoid the negative implications some interviewees were concerned about.

5.3.6 Management Strategies

5.3.6.1 Management strategies suggested by interviewees

Interviewees were asked several questions about potential precautionary management strategies for pharmaceuticals in the environment. Sixty-seven percent of the interviewees felt it was very or somewhat important that their government take management action to reduce the release of pharmaceuticals to the environment (Fig. 5.7). They cited mainly evidence of environmental impacts of PhACs, such as the feminization of fish by 17α-ethinylestradiol, as a basis for wanting management action.

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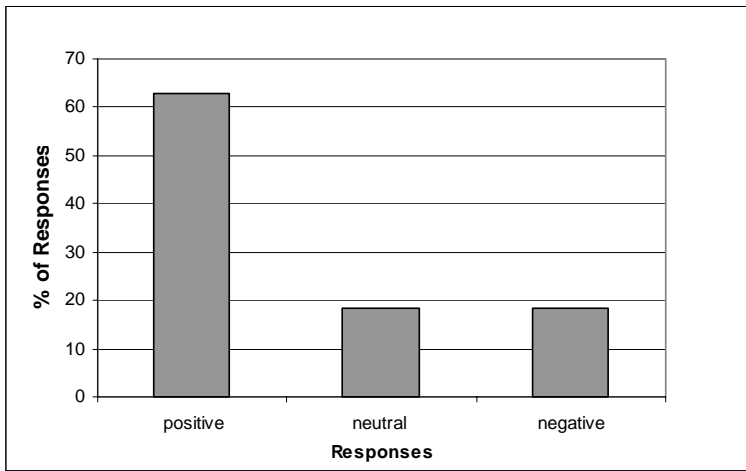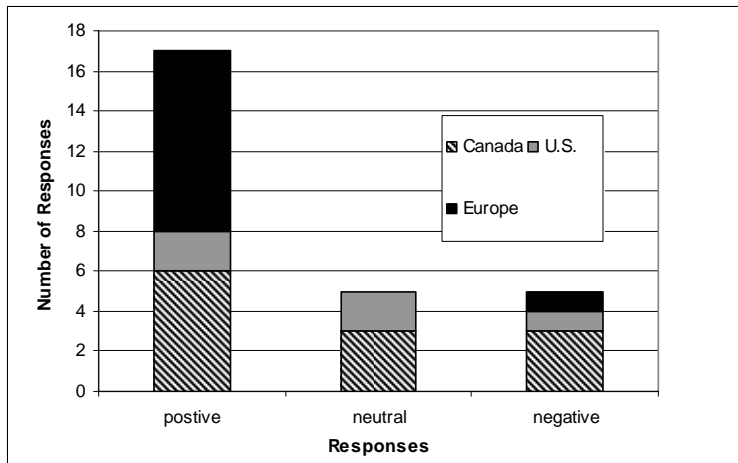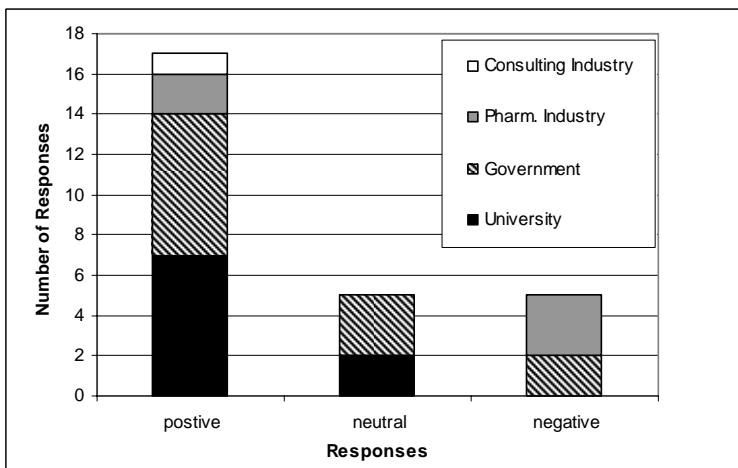
Figure 5.6. Views of the precautionary principles, as expressed by a) all interviewees, b) interviewees according to location, c) interviewees according to sector.

Positive	Neutral	Negative
"I think the appropriate application of the precautionary principle with the intention of the Preamble of CEPA and Rio is very appropriate." – *Interviewee 1*	"The precautionary principle sounds good on paper, but you're still right back in the decision making process." – *Interviewee 3*	"Probably, I do not support the precautionary principle…we need to be able to make connections between the release of compounds and environmental effects." -- *Interviewee 10*
"I think you have to, to a certain extent, depending on the agents, and their ability to alter ecosystems. Some of these agents are pretty powerful and long-lived in nature, and as such we might not have all the evidence, we might not have all the pieces of the puzzle, but I think you have to assume certain things, where science isn't available." – *Interviewee 12*	"I'm kind of middle of the road on it. I don't think that perceived risk with the number of issues that are out there, I think it's not a value added exercise to try to address every perceived risk without having at least some measure of certainty." – *Interviewee 11*	"No I do not. Again, that's based on the use of our public dollars." – *Interviewee 15*
"Yes, very much. From a scientific point of view the precautionary principle is something that is not always, where you take positions which are not always based on research and data that you have obtained via research work. But as a member of this society, I wouldn't like not to rely upon the precautionary principle, because you never know what might happen. And if you have indications that there is some hazard to yourself or to the environment, one should take action." – *Interviewee 27*	"Different people interpret the precautionary principle in different ways. My feeling is that all risks need to be balanced versus economic costs and other risks. I don't know if I can give you a yes or no answer." – *Interviewee 7*	"They don't know what they're doing and it's very complicated what to do as a result of saying such a thing. Precautionary principle." – *Interviewee 22*
"Basically yes, but if such concerns can be reasonably ruled out, then restrictions should be loosened." – *Interviewee 25*		"I think it's actually a very dangerous principle." – *Interviewee 26*
"Yes – It is better to avoid environmental problems than to mediate after the fact." – *Interviewee 5*		
"Yes, yes, yes!" – *Interviewee 19*		
"Yes I do because time is irreversible and restoring is always much dearer than acting proactive." – *Interviewee 9*		
"To a point, yes. When there's demonstrated low-level effects in model organisms, one has to assume that it would be true for other organisms." – *Interviewee 6*		

Table 5.6 Interviewee responses to the use of the precautionary principle in environmental decision making, categorized as positive, neutral, or negative.

Proportionality of precautionary action	Definition	Socio-economic balance	How much evidence is enough?	Other
"It doesn't mean you ban chemicals; it means you take an action, an appropriate action. Some people interpret the precautionary principle as in if there's any uncertainty, you ban it. And that's a very inappropriate response." – *Interviewee 1*	"The Rio Declaration, paragraph 15, is unintelligible and you cannot use it in public policy making." – *Interviewee 2*	" We need to consider social and economic impacts." – *Interviewee 10*	"The question is, it's still a grey area around how much information is enough…what's the appropriate time to jump in?" – *Interviewee 3*	Adaptivity: "If such concerns can be reasonably ruled out, then restrictions should be loosened." – *Interviewee 25*
" If we put rats in an environment and then just fill it up with completely 100% of this particular compound, there's an additional incidence of cancer of say 1 in 100. Well yes, that's true, do you take that to the nth degree and say we have to remove this completely from the environment because it's a carcinogen?" – *Interviewee 11*	"People need to very clearly understand what they mean by precautionary principle. And precautionary principle is defined in different regulations and different international agreements slightly differently. And that makes a huge difference in whether or not you …what you think of what the precautionary principle is." – *Interviewee 1*	" With limited resources, you have to reallocate some of them to these issues, and you take away from issues that are maybe more of an issue." – *Interviewee 11*	"The precautionary principle should apply when there's doubt about a risk, but before you are allowed to have doubt you have to investigate, so you have to make risk assessment, and then if you're left with questions of uncertainty, then …you can go and you can say, then we don't want it, because we don't know." – *Interviewee 18*	Stakeholder participation: "All stakeholders have to be informed properly so that they can act properly." – *Interviewee 9*
"What can you possibly do to somebody who needs to take a medicine?...Let's assume it does something to the environment, let's say if you think of a million people taking Advil all across the country, what possibly could Health Canada do that would solve the problem?" – *Interviewee 22*	"I think that the appropriate application of the precautionary principle with the intention of the preamble of CEPA (Canadian Environmental Protection Act) and Rio is very appropriate." – *Interviewee 1*	"No I do not [support the use of the precautionary principle]. Again, that's based on the use of public dollars." – *Interviewee 15*	"All the examples I read are times where with hindsight you should have used the precautionary principle. So I don't know at this stage, how serious it has to get, that you use it up front." – *Interviewee 20*	Dialogue/ Debate: "You need a dialogue, where people can actually have a debate, raise the questions." – *Interviewee 26*
"There's some people who say, you must not do anything because you don't know what the future holds…If the guy who invented immunization was around today, the precautionary principle wouldn't allow it to be developed. You don't know what immunization might do to people. But how many people's lives have been saved, and the quality of that?" – *Interviewee 26*	" The thing about the precautionary principle is that there are already diverging opinions about what it really means, how to use it." – *Interviewee 18*	"My feeling is that all risks need to be balanced versus economic costs and other risks." – *Interviewee 7*	"The real question is how robust is the scientific evidence on which to base judgement as to environmental risks/threats for various types of drug molecules." – *Interviewee 23*	

Table 5.7 Examples of interviewees' concerns about the precautionary principle, divided into categories.
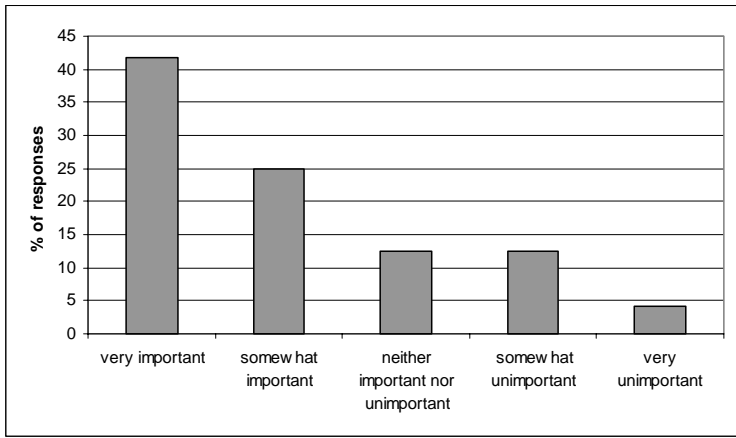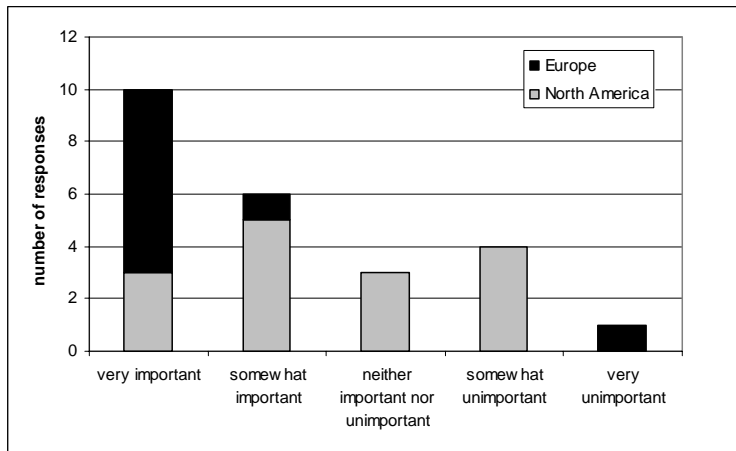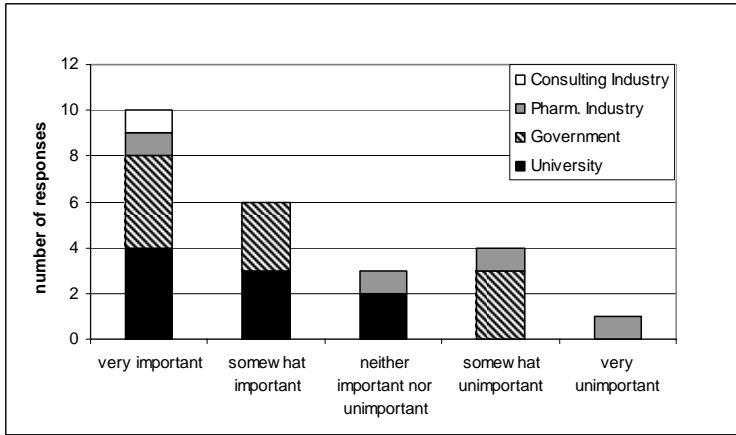
Figure 5.7. Interviewees' responses when asked how important it was to them that their governments take action to reduce the release of pharmaceuticals to the environment. a) percentages of total number of responses, b) number of responses in each category according to geographic location, c) number of responses divided according to sector.

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Interviewee 7 summed up his reasons for recommending management action: "I think there are some legitimate concerns about ecosystem protection, aquatic ecosystems, especially in effluent dominated waters." Some also felt that it was important to act to address public concerns: "We should be concerned regardless of toxicology because of wastewater recycling and risk perception issues – it's a social psychology issue" (Interviewee 14). Some of those who did not feel it was important for their government to take management action at this time argued that scientific evidence of the environmental impacts of PhACs was insufficient; for example, Interviewee 1 stated:

> I think it's critically important that we do the science to support the risk assessment, and we shouldn't take any major action until we know what those risks are... We need to make risk-based decisions and we don't have the tools to assess those risks at this point in time, appropriately.

Others felt that the costs of management action would be too high; Interviewee 15 explained, "It's difficult to expend that money when there's so many other priorities. I think that the public health could be better served through other aspects." There was also concern that management action might entail inappropriate restrictions on the availability of medications:

> If you were to act prematurely, you could find that you are actually leading to the withdrawal, thought the political process, of very important medicines for people with actually no significant environmental impact at all. And what are you going to follow them up with?...the idea is, if you're going to make decisions about risk management, surely we want to try and make decisions based on knowledge, not on ignorance, and certainly not on fear. And for that reason I think it would be premature and irresponsible. (Interviewee 26)

These concerns reflect several of those voiced in relation to the precautionary principle; it is essential that management action remain proportional, balanced, and account for costs, financial and otherwise.

The interviewees advocated a number of risk management strategies for PhACs in the environment. Table 5.8 lists management strategies favoured by the interviewees, and the number of interviewees who suggested each management strategy. The most

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popular risk management strategy among the interviewees was the implementation of returns programs for unused/expired medications, coupled with public education about the need to return drugs rather than throwing them down the toilet or in the garbage. Although the contribution of improper pharmaceutical disposal to the environmental loading of PhACs is not well understood – and is generally believed to be minor (Heberer, 2002) – Interviewee 16 explained why this was seen as such a positive management response: "I don't think there's a good feeling for how much of what we find in the environment is coming from disposal of unused and expired medication, but I it seems like a logical, easy portion to remove." Many interviewees advocated risk assessment regulations as a basis for further management action, such as labelling, or substitution of more environmentally harmful drugs for less harmful ones. They also cautioned, however, that current, traditional risk assessment methods are inappropriate and insufficient – better methodologies must be developed for this to be an

PhAC Management Strategy	Times Suggested
Pharmaceutical returns programs & public education for proper disposal	13
Risk assessment regulations	8
Improvement of wastewater treatment technology	6
Environmental labeling of PhACs (for use and disposal)	4
Reduction of consumption/over-prescription through education of medical professionals and public	4
Development of 'green' pharmaceuticals (better targeted, more biodegradable, etc.)	3
Improvement of drinking water treatment technology	2
Substitution of drugs with lower environmental risk for those posing greater risk	2
Dilution: reduce water use	2
Best management practices in agriculture	1
Improved treatment of industrial wastewater (pharmaceutical industry)	1
Environmental monitoring of PhACs	1
Source water protection regulations for agriculture	1

Table 5.8 Risk management strategies for PhACs in the environment, suggested by interviewees.

effective means of addressing PhACs in the environment. Interviewee 2 suggested, "that researchers use risk assessment for this like for most other things, but we should ask the right questions and we should answer the right questions with the right tools, and we're not doing that right now." Improving wastewater treatment facilities was also a popular option, partly because it was seen as relatively effective, but also because it addressed several sources of water contamination:

> [One strategy would be] to come up with guidelines around the treatment of domestic wastewater, so that you're removing these compounds. Mind you, I mean, that relates to a whole bunch of problems that we're having in terms of discharges of untreated or inadequately treated wastewater here in Canada. I mean, most people are appalled, in Europe at least, that there's places like Halifax, St. John's, Victoria, and other cities, Montreal, in which there's just primary sewage treatment, so it's not only just the pharmaceutical issue, it's a whole range of issues around adequate treatment of our domestic wastewater.
> (Interviewee 3)

The variety of strategies advocated by the interviewees suggest that they feel a mixture strategies addressing the various stages of the life cycles of pharmaceuticals should be used in management.

5.3.6.2 Views of Potential Management Strategies

In addition to asking which management strategies were favored, without being prompted with any particular strategy, interviewees from the government and academic sectors were asked to respond to a list of strategies both qualitatively, and with a quantitative scoring of strategies based on according to effectiveness and feasibility. Fig. 5.8 illustrates the scoring of management strategies based on effectiveness and feasibility. Pharmaceutical industry interviewees were asked to respond to a similar list based on the perspective of the industry, but as most were reluctant to give quantitative scores, only their qualitative responses are discussed in this thesis. Advanced wastewater treatment scored highest in terms of effectiveness, with an aggregated score of 8.0 out of 10 (Doerr-MacEwen & Haight, 2006); this is not surprising, as the literature indicates that treatment methods such as ozonation and membrane filtration can achieve removal rates of more

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than 95% for most PhACs (Heberer, Feldmann, Reddersen, Altmann, & Zimmerman, 2002; Sedlak & Pinkston, 2001; Ternes et al., 2003; Zwiener & Frimmel, 2000), compared with an average of 60% for secondary wastewater treatment plants (Ternes, 1998). Interviewees pointed out that advanced treatment methods would be especially appropriate in large municipalities producing high volumes of waste, with existing infrastructure to support the advanced technology (Table 5.9). They also raised concerns, however, relating to the expense and energy requirements of the technology, the end-of-pipe nature of the management strategy, and the potential for generation of reaction
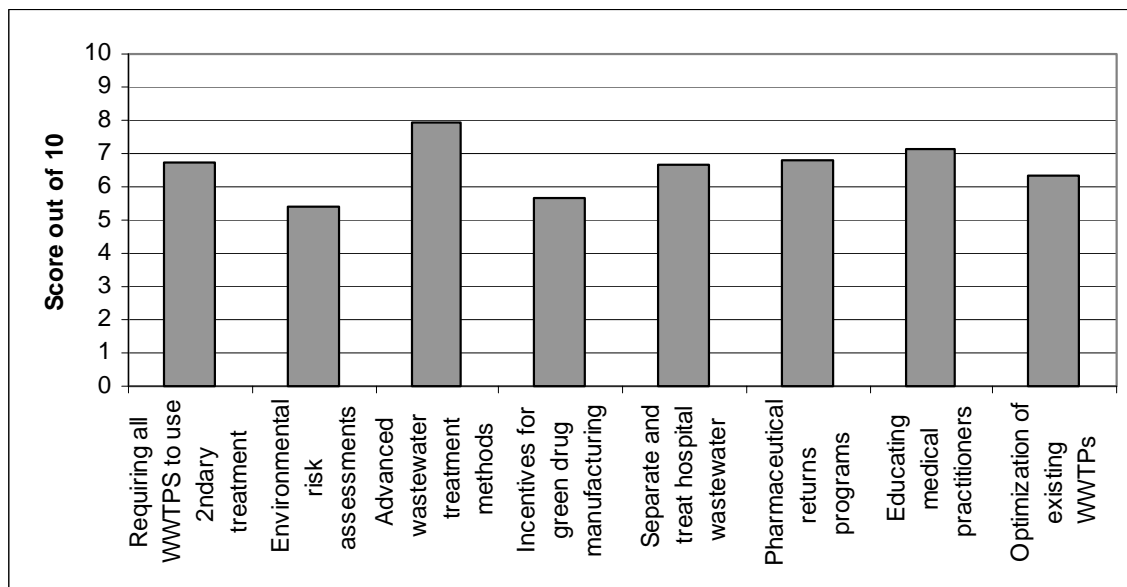
Figure 5.8. Aggregated scoring of management strategies by interviewees, according to effectiveness in mitigating the possible environmental impacts of PhACs.

products, among other concerns. Many of these concerns are reflected in the scoring of advanced treatment methods in terms of feasibility (Fig. 5.9); it ranked second to last among the management strategies, with an aggregated score of 4.9 out of 10.

Reducing the consumption of pharmaceuticals through education of medical professionals, to minimize over-prescription, was rated the second most effective option (Fig. 5.8), with a score of 7.1. This option may have scored highly because consumption of pharmaceuticals is the main route through which PhACs enter the environment (Heberer, 2002) and because reducing consumption addresses the problem in a proactive way, rather than being an end-of-pipe solution. Education of medical professionals was

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seen as moderately feasible, being ranked 5th out of 8 management strategies (Fig. 5.9), with a score of 6.7. Interviewees were uncertain of the feasibility of convincing doctors to reduce over-prescription when they are subject to so much advertising on the part of the pharmaceutical industry. One interviewee from the industrial sector suggested the pharmaceutical industry was unlikely to see a need to reduce rates of drug consumption (Table 5.10).
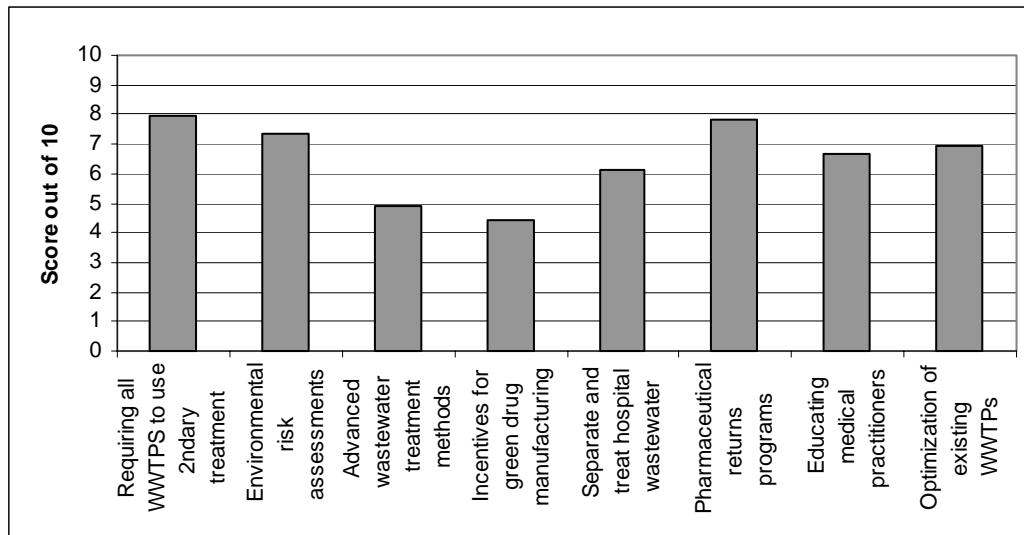
Figure 5.9. Scoring of risk management strategies for PhACs in the environment by interviewees, according to feasibility.

Positive Aspects/Benefits	Negative Aspects/Concerns
Useful if pre-existing infrastructure good: "It depends on the location. If you have a very good system set up in Toronto or somewhere else, you have basically all the wastewater being treated, you have already some good infrastructure, you have a good treatment facility, you can put that in, ozonation, and it has been shown that it does remove pharmaceuticals and other contaminants as well." – *Interviewee 2*	**Ineffective if pre-existing infrastructure lacking:** "I use the analogy you don't put on a fancy filter on a leaky bucket. You know, you want to fix that first, make sure that you don't have a lot of storm runoff and straight line piping where you send untreated sewage into the environment and stuff like that, and then you start worrying about these things." – *Interviewee 2*
Useful for large municipalities: "I think at least selectively, I don't know if we would want every single wastewater treatment plant everywhere to do that. Maybe you could phase it in, maybe…start with the volume of waste. So if you're a town or 300, compared with a town of 3 million…" – *Interviewee 16*	**End-of-pipe solution, does not address other sources of PhAC contamination:** "Even if you spend loads of money improving your wastewater treatment plants, you can have other sources that can contaminate the surface water… it's always better to look at the source of your contaminants than to do with kind of end of pipe procedure." – *Interviewee 27*
Useful for effluent-dominated waters: "May prove to be essential on some works with low dilution in the receiving watercourse." – *Interviewee 21*	**Treating drinking water may be preferable:** "I would lean more towards ozonation for drinking water treatment." – *Interviewee 5*
Effectively removes PhACs & other contaminants: "I certainly think that most of the way we should deal with this is better treatment. That's my overall impression that that's the way to deal with it. Because there's so much other junk that's going through there, that people put down, and you know they may not be pharmaceuticals products, they could actually be antifreeze, it could be brake fluid. People pouring it wherever they pour it." – *Interviewee 22*	**No systems can get rid of PhACs entirely:** "We tested a system, one of the most advanced systems in the United States, where they used a series of membranes including reverse osmosis. After reverse osmosis … there are some pharmaceuticals that make it completely through there. Now the levels are low, they're very much attenuated. But if you're not going to look at toxicology, you're going to say, 'if I detect this at any concentration it can't be there', you'll never win; there's no treatment process capable of removing things to the atomic level." – *Interviewee 15*
	May produce reaction compounds with unknown environmental impacts: "Ozonation, the results show it can be successful, but the problem is the production of reaction compounds, new products." – *Interviewee 8*
	Expensive and politically unpopular: "Very expensive. Leads to increases in peoples bills so not politically popular." – *Interviewee 21*
	Environmental impacts of energy use to run upgraded plants: "What we have to try to do, as the environmental portion of the company, is to think holistically about these things. And if the environmental impact was greater on the atmosphere, because of running much higher complexity and more energy expensive wastewater treatment plant, with no environmental benefit, why do it? To me that would be a step backwards." – *Interviewee 26*

Table 5.9 Interviewees' comments on advanced wastewater treatment technology.

Positive Aspects/Benefits	Negative Aspects/Concerns
Help medical professionals to consider environmental impacts: "Education programs aimed at medical communities would encourage doctors and vets to think more about antimicrobial resistance and environmental impacts." *– Interviewee 10*	**Cannot compete with marketing by pharmaceutical industry:** "I don't think it would work very well. Over-prescription is driven in the U.S. by advertising and I think that the environmental concern is not going to affect that." *– Interviewee 7*
Allows for substitution of more environmentally friendly drugs: "I think that's appropriate, again it's management strategies that probably could be easily implemented and you could take that a step further and say well, at some point in time if you identify a bad actor, not ban it necessarily, but say if it's an either or situation, here's the one that's environmentally friendly. So equipping physicians to make an appropriate decision is a good thing." *– Interviewee 11*	**Need very early education to have an effect:** "The education comes so often from the pharmaceutical industry to practitioners. There's that sort of, you come into a practice, and you adopt a practice norm in terms of pharmaceutical use. And what's there to alter that? Usually it's a pharmaceutical rep that comes in and says, here's this wonderful drug. So it's tough, I think there has to be a very strong education program back at the veterinary or medical school; an early level of education." *– Interviewee 12*
Government supports as part of health & environmental education: "Part of the education process, Health Canada tries to promote knowledge and promote best practices; Health Canada would be for this." *– Interviewee 13*	**Industry does not feel medical practitioners over-prescribe**: "The industry is going to be very cautious to make it appear that their customers are abusing their drugs, so I think they're going to say, but we do that in our labelling, we give very specific instructions as to how drugs should be used." *– Interviewee 24*
Beneficial to human health: "Good idea for human health, not just pharmaceuticals" *– Interviewee 14*	**Patients demand drugs**: "[It is] important to reduce quantities of pills sold…the problem is, patients want prescriptions." *– Interviewee 8*

Table 5.10. Interviewees' comments on education of medical professionals to reduce pharmaceutical consumption, as a management strategy for PhACs in the environment.

Pharmaceutical return programs coupled with public education regarding drug disposal, was ranked 3rd in terms of effectiveness, together with requirements for secondary wastewater treatment, with a score of 6.8. This is in some ways surprising, as pharmaceutical disposal is considered a minor contributor to the environmental loading of PhACs, as some interviewees pointed out (Table 5.11.) The score may reflect interviewees' support for returns programs for a variety of reasons, including public awareness. Pharmaceutical returns programs were ranked 2nd in terms of feasibility (Fig. 5.9), with a score of 7.8. Many European interviewees indicated that their countries already have returns programs (Table 5.11) and while legal barriers may make such programs less feasible in the U.S. (Table 5.11), their legislated existence in the Canadian province of British Columbia (Government of British Columbia, 1997) suggests they could be more extensively used in Canada.

The lowest score in terms of effectiveness was given to environmental risk assessment regulations, with a score of 5.4. This is somewhat ironic, as appears to be the only management strategy, other than research, in which many governments currently are officially engaged (Section 5.3.4.2) (CPMP, 2001; FDA, 1998; Health Canada, 2002), and was the second most popular suggestion as to risk management strategies among the interviewees. This may reflect a dichotomy between the ideal capacity of risk assessment, in terms of producing an understanding of the risk of PhACs and the real effectiveness of the process. As many of the interviewees have a scientific background, they value the rational, science-driven basis for management provided by risk assessment. For example, several interviewees, including Interviewees 1 and 26, iterated several times throughout the interview, the need for a "risk-based approach" to the management of PhACs in the environment. Some of these positive views of risk assessment are shown in Table 5.12. As experts on pharmaceuticals in the environment, however, the interviewees also recognize that traditional risk assessments do not address the questions they are asking regarding pharmaceuticals in the environment: What are the chronic, sublethal effects? What are the effects of mixtures (see Section 5.3.3)? Furthermore, the interviewees involved in management recognize that the risk assessment

Positive Aspects/Benefits	Negative Aspects/Concerns
Effects on public awareness: "I think it's a good program. I think it will have a minor impact on the actual release of pharmaceuticals into the environment. But it's going to have a big impact on public perception of environmental issues." – *Interviewee 1*	**Must ensure proper disposal after return**: "As long as they're taking care of it in an appropriate way. You know, yeah, I take it back and they put in a landfill that has no leachate collection system, and guess what? Or that does have a leachate collection system and then pumps it back into the wastewater collection system!" – *Interviewee 11*
Would be used by public: "If that could be implemented it would probably be something that the general public would use. Everyone's got stuff up in the cupboard that it's been there for a while, and I'm never going to use it again, and it kind of sits there for ten years." – *Interviewee 11*	**U.S. law makes returns difficult:** "The U.S. is different – the law says you can't return drugs to the pharmacy because of the Controlled Substances Act; you can't transfer controlled substances to anyone that the substance wasn't prescribed to. U.S. pharmacies contract with reverse distributors but not for anything that was in consumers' hands. Maine has passed legislation for mail returns program but they don't have the money to do it." – *Interviewee 14*
Legislation of returns programs creates level playing field for industry: "Right now for pharmaceuticals, we are paying a fee for getting rid of the containers in Ontario. Not yet for the contents. If you legislate it, it will work. It can't be voluntary. Because voluntarily you'll get all kinds of different companies giving reasons why I should only pay 0.1, and you should pay 0.3." – *Interviewee 22*	**Questionable success of public education**: "You know, human nature, I don't know, I'm often quite sceptical of these public education campaigns. They often show effectiveness right after, and then someone looks back in a year and they're reversed." – *Interviewee 12*
Especially helpful for products like patches and creams: "Yes, it may help to some extent. In particular when it comes to containers, administration routes, patches or creams. With above all hormones. Because the fraction that is absorbed is very small, it's a few percent in a week or so." – *Interviewee 19*	**Limited effect on environmental concentrations of PhACs:** "That won't help at all. I'm working with PHR, the pharmaceutical manufacturers' association. And they've already done this calculation, and it would not change the concentration in the environment at a measurable level. The amount of things dumped down the toilet is so small, compared to the amount ingested, especially for the new pharmaceuticals." – *Interviewee 15*
Good for child safety: "There is a program here in Germany, that private households are asked to return their pharmaceuticals to the pharmacist. I think this has been set up because of safety reasons, for children, to make sure that the risk for children to take some pills is reduced." – *Interviewee 27*	
Public eager to engage: "Already done in Spain: people are very active once the problem is explained to them." – *Interviewee 8*	

Table 5.11. Interviewees' comments on pharmaceutical returns programs together with public education as a management strategy for PhACs in the environment.

Positive Aspects/Benefits	Negative Aspects/Concerns
Detects substances with acute effects: "I think that the systems we have are good at picking up any immediate effects; immediate effects would be picked up by the assessments. We build in safety factors, we use reasonable worst cases, and we use assessment factors to adjust for different species." – *Interviewee 20*	**Existing risk assessment methods inappropriate:** "We need to ask the right questions, answer the right questions with the right tools, come up with the right answers. We don't do that very effective right now… If you look for new problems in an old-fashioned traditional way, you're not going to find them." – *Interviewee 2*
Creates fair playing field for industry: "What's very important is for commerce and for innovation, is to have that actually working on a level playing field, so that the different pharmaceutical companies are able to work to the same standard, and innovate to the same context. So there is a role for transparent, sensible environmental regulation and its application." – Interviewee 26	**Red tape & ignores real-life conditions:** "You're taking it in isolation from other compounds and the actual real environment, I mean you're not going to go out and do that kind of environmental impact assessment at environmental conditions. So one of the down sides is it certainly adds more red tape to the overall approval process." – *Interviewee 3*
Helps develop management strategies: "There could be a case where you're wanting to manufacture a drug, where you gather information as you're required to do by law…[and] using information on the ecotoxicology of drugs or on its fate in the environment to help you design a wastewater treatment plant." – Interviewee 26	**Real-life conditions not accounted for:** "They may be looking more at acute effects, whereas long-term chronic low-level is really more of a concern. What we haven't mentioned today is the mixture issue – throwing a bunch of low level compounds together as a mixture in a stream, may have some unanticipated effects. My current understanding is that it wouldn't test for mixture effects. It's still a good idea, I just am not sure it would catch all the unanticipated effects." – *Interviewee 16*
Helps develop management strategies: "The legislation states that it is intended to be used for labelling. So you have to make a risk assessment, and where necessary or where possible, indicate how this risk can be reduced as much as possible… If you have the data, authorities can use it to make their management decisions."– *Interviewee 19*	**Futile to try to prove absence of risk:** "On an epistemological side, [there is] also the impossibility of rigorously proving the absence of risk with tests and strategies developed for evidencing the presence of effects (there will never be any certainty about safety)" – Interviewee 25
	Banning not possible, so no clear management outcome: "For human pharmaceuticals in Europe, the directive says, banning a compound for environmental reasons, is not allowed, is not possible, for ethical reasons. But what are you going to do with that information, that's what I mean, there's no clear scheme with regards to risk management." – Interviewee 27
	No clear management outcome: "Nobody's found a practical control at the end, what you would do. Are you saying you would actually not approve a medicine? So you're submitting data, people are spending time, effort, energy getting all these documents, and then they just approve it anyway." – *Interviewee 22*
	Many PhACs below assessment cutoff level "Most pharmaceuticals don't exceed the 1 ppb cutoff, so they don't get assessed" – *Interviewee 14*

Table 5.12. Interviewees' comments on risk assessment regulations.

regulations exist without a clear purpose; the assessment process is not linked to any management outcomes (Table 5.12). Thus, while implementation of risk assessment regulations is seen as feasible (Fig. 5.9), it is understandable that the interviewees believe risk assessment as it exists now is ineffective, but that it has potential as a future management strategy, as indicated by their responses in Section 5.3.6.1.

Incentives for the development of 'green drugs' were ranked as 7th out of 8 in terms of effectiveness, and last in terms of feasibility, with scores of 5.6 and 4.4, respectively. The view that this strategy was ineffective and infeasible was not shared by all interviewees, however, as individual effectiveness scores ranged from as low as 0.5 to as high as 10, and feasibility scores ranged from 0 to 10. The strong, polarized opinions on incentives for 'green' drug development are reflected in Table 5.13, with Interviewee 1 calling the management strategy "naïve", while Interviewee 13 called it a "great idea" (not shown in Table 5.13), and two interviewees from the pharmaceutical industry stated that the development of 'green' pharmaceuticals is already being pursued by the industry.

The remaining management strategies, all involving some aspect of wastewater treatment, received moderate scores in terms of effectiveness and feasibility. Requiring all municipal WWTPs to have secondary treatment as a minimum, treating hospital wastewater separately with advanced methods, and optimizing existing wastewater treatment plants without upgrading technology, were all seen as similarly effective, with scores of 6.8, 6.7, and 6.3, respectively. Interviewees suggested that each of these strategies would contribute somewhat to reducing the release of PhACs to aquatic environments, but that they would not be sufficient to prevent the bulk of the environmental PhAC loading (Tables 5.14, 5.15, 5.16). In terms of feasibility, requiring all municipal WWTPs to use secondary treatment as a minimum, received a high score of 7.9 to rank first among the management options. European interviewees explained that secondary treatment was already required in their countries. Many North American interviewees felt that as secondary treatment was already widespread, it would be feasible to upgrade those remaining WWTPs to secondary treatment (Table 5.14). Others,

Positive Aspects/Benefits	Negative Aspects/Criticisms
PhAC manufacturers, like manufacturers of other substances, responsible for preventing impacts: "They [drug manufacturers] should be encouraged to look in these directions, and I think that they will. I mean they will realize that they are producing chemical in relatively large amounts that will be released into the environment, just like a number of other industries, and they will have to take that into account." – *Interviewee 2*	**Drug development process too complex and difficult:** "It's a naïve idea. The drug discovery process is extremely complex and extremely serendipitous, and to think that we're going to be able to fund people to find green drugs is a needle in a haystack." – *Interviewee 1*
Addresses environmental concern at source: "You've got to get to the source of the problem and make sure that you produce environmentally safe products like for anything else. Then you don't have to worry so much about effects and treatment." – *Interviewee 2*	**Drug development process too complex and difficult:** "If it was possible, yes maybe, but I don't think we realize the complexity of trying to come up with something that has a certain affinity for receptors in the body, certain blockage, and then trying to say, "How can I change the molecule so it's still effective, still interacting with this receptor, but also biodegradable?". I do not see that as a viable option." – *Interviewee 15*
Green pesticides exist, so green drugs can be made: "It would be possible to do from a scientific perspective because has been done with pesticides; the pesticide industry now makes rapidly degrading substances." – *Interviewee 17*	**Drug development process too complex and difficult:** "Extremely difficult already to find a molecule that does a defined job, has low incidence of adverse effects and other attributes for a 'good' pharmaceutical; adding further requirements will considerably reduce success chances." – *Interviewee 25*
Toxicity and biodegradability can be changed: "The industries will see that there's ways that they can either reduce the toxicity of the compounds or increase the biodegradability of the compounds and don't get high exposures in the environment." – *Interviewee 2*	**Drug development process too complex and difficult:** "The problem is what's degradable in the environment is going to be rapidly degraded in the body. So you'd have to develop drugs that would be effective quickly, which means more potent, which means more risk. So this is the problem that we face, and it may not be resolvable." – *Interviewee 6*
Include all ingredients in environmental considerations: "It's important…all ingredients should be looked at, not just the active moiety." – *Interviewee 8*	**Drug development process not driven by environmental concerns:** "I think it's very unlikely that it would work. I think the drug development process is driven by a lot of other things, there's a lot of money that goes into that, so I think you'd have to offer large incentives to get them to do that. So they're going to do what they're going to do anyhow." – *Interviewee 7*

Table 5.13. Interviewees' comments on incentives for the development and manufacturing of 'green' drugs. Continued on next page.

Means of administering drugs can be made 'greener': "New application methods like the use of patches, smaller packages, more specific prescriptions, for example gender-specific doses, are needed." – *Interviewee 17*	**Drug development process too complex and difficult:** "It's a hard thing to find a good drug now. And if we had the potential to do it, we would do it. Because we'd love it. It would be great for us, if you could find such a thing, it's good. But I'm saying it's so hard right now to find drugs that work, that pass all the tests, that get approved by FDA, by the government of Canada, it's so hard to find stuff like that already."– *Interviewee 22*
Image concerns will drive manufacturers to produce 'green' drugs: "I think the funny thing is that the pharmaceutical companies, and the researchers, they are actually greener than the governments are. So they are actually, they have a lot of good thoughts and are really researching to make this work. It think it's also in the market it's better to be green, good for your health. It's something they are quite afraid of is of having a name, saying that it's a very bad drug. Because if it's bad for the environment, how good can it be for health?" – *Interviewee 18*	**Drug development process too complex and difficult – consider other forms of green chemistry:** "I think that it's a very very complex area, and as a scientist, I think we should be very sober about what science can deliver in this area. But there's an aspect of this question that I think is much more tractable, and that's actually greening, making more green, the total production process of drugs. This is basically what green chemistry is. This process of trying to build environmental considerations into your drug development processes, as much as possible." – *Interviewee 26*
Market forces will drive production: "I think it's the market that drives it… Often, I've noticed the companies that are trying to develop these are small, independent groups that would never have much of a market share… they will develop in order to meet the market need."– *Interviewee 12*	**Not as easy as people think:** "So I think it's a bit of a holy grail, this idea, from an honest scientific opinion, I think it actually could be a holy grail. And what I'm a bit scientifically nervous about is when these articles get published in some journals, some people think that it's easy. They really think that finding safe new medicines is easy."– *Interviewee 26*
Regulatory concerns will drive development of 'green' drugs: "I know the companies are concerned about having to provide phase 2 data [because of risk assessment regulations], it's an extra development cost. So I think if they could develop greener products, if you like, which in our case would stay in phase 1 [of the risk assessment], then you wouldn't need to give them any incentive other than to point that out to them."– *Interviewee 20*	**Drug development process too complex and difficult:** "Structure and function are inextricably linked. The attrition rate for drug candidates is already very high based on safety, efficacy, stability and manufacturing requirements. Adding yet another requirement with respect to biodegradability for the structure of these molecules will probably result in a massive increase in the attrition rate of drug candidates." – *Interviewee 23*
Incentives may convince manufacturers to invest in developing 'green' drugs: "I think in the short term, one of the most effective things that one could do would be to look at those classes of products that appear to present the largest potential problems: statins, beta blockers, estrogens, and offer commercial incentives for organizations to come up with new products that would have reduced environmental impact." – *Interviewee 24*	
Green drugs already being developed: "We are already developing and marketing several such active substances." – *Interviewee 25*	

Table 5.13. Continued from previous page. Interviewees' comments on incentives for the development and manufacturing of 'green' drugs.

Positive Aspects/Benefits	Negative Aspects/Criticisms
Lower environmental concentrations of PhACs than without secondary treatment: "I think that secondary treatment should be a minimum standard, for a lot of reasons. If we don't have secondary treatment, you will have a hundred to a thousand times higher concentrations of pharmaceuticals in the environment, so, yes, secondary treatment is critical in the management of pharmaceuticals." – *Interviewee 1*	**Financial strain for municipalities:** "It comes down to money. Municipalities are responsible for investing in it, and without some incentives for providing the funding to municipalities, I think that's going to be a problem."-- *Interviewee 3*
Improving water quality in general: "I would think that it would be desirable that all systems at least have secondary treatment but that would achieve additional objectives other than dealing with these classes of substances." – *Interviewee 4*	**High financial cost:** "Last time we looked at it in detail, in the late 80s, it was about 4 billion dollars for Ontario to come up with secondary treatment. It's probably significantly less than that now, because a lot of systems have gone that way. But to require it to deal with PPCPs wouldn't be value added." – *Interviewee 11*
	Little change in PhAC concentrations compared to current levels: "If you're looking at a national issue, no it wouldn't help at all, because everyone almost already has secondary. So at a national scale it wouldn't make at a big difference. Not at a broad scale." – *Interviewee 15*

Table 5.14. Interviewees' comments on requiring all WWTPs to use secondary treatment as a minimum.

Positive Aspects/Benefits	Negative Aspects/Criticisms
Easy to implement and cost effective: "I still think optimizing existing treatment systems once the priorities are identified would be an option that could be readily implemented and very cost-effective. If you identified that a certain compounds was really, was a compound of concern, and you could triple its removal by increasing your SRT, solids retention time in the plant, if the negative impacts of doing that were not as much of a concern, why wouldn't you do it?" – *Interviewee 11*	**May not be effective:** "Some drugs pass through the STP without being affected at all, and others are degraded to some extent. For those that are degraded of course, a longer retention time would be sufficient. But I think it's a half-efficient method." – *Interviewee 19*
Can address several environmental contaminants: "Yes, it's a great idea. Again, a lot of these things tie in and happen at the same time; if you're getting lower BODs, CODs, lower nutrients, you're probably getting lower pharmaceuticals too. You know, in general there's a few compounds that are pretty sneaky at getting through, but in general that's what I always suggest to our utilities, do the best you can. Deal with what you've got, try to keep your SRTs and things like that as high as you possibly can, yes I think that's a good idea."– *Interviewee 15*	**May not be effective:** "I really don't know how well that works and how much room there is for optimization. The plants aren't really made to get rid of pharmaceuticals." – *Interviewee 18*
Cheaper option than upgrading technology: "An obvious choice before going to the expense of an upgrade." – *Interviewee 21*	**Must be sure not to sacrifice other treatment objectives:** "Consistent with meeting other treatment objectives, that's only one objective." – *Interviewee 4*

Table 5.15. Interviewees' comments on the optimization of existing WWTPs.

Positive Aspects/Benefits	Negative Aspects/Criticisms
Important for harmful or persistn PhACs like antineoplastics: "Some of the anti-cancer drugs and some of the contrast media, things like that, are things that I think we should be concerned about from hospitals. It doesn't have to be a big complicated system, you just do some pre-treatment which may then allow a sewage treatment plant to do the second part of the job." – *Interviewee 1*	**Many PhACs used outside of hospitals:** "I think that what we're seeing is a lot of general use across the broad and it's certainly not going to be in the hospitals, it's going to be in clinics, it's going to be in the home, some of these advanced drugs they take them at home, chemotherapy, is at home, so having a treatment system in the hospital won't help you." – *Interviewee 11*
Important for persistent compounds & those used largely in hospitals: "Good idea because some compounds appear in hospitals only and are difficult to remove, like iodinated contrast media…some compounds like antibiotics are produced on a large scale in hospitals." – *Interviewee 8*	**May not help at national scale:** "Would it help the loading on a national level, I don't think so, but I think there are advantages to doing it beside the pharmaceuticals." – *Interviewee 15*
Already exists in Europe: "That's already occurring, and least in Europe, hospitals have to have their own sewage treatment, their own wastewater treatment, enhanced." – *Interviewee 2*	**May be more effective to improve municipal WWTPs**: "In Germany cytostatics must be incinerated… for other aspects in hospital, there are not necessarily more medications used, plus it would be more useful to target the big picture with municipal wastewater treatment plants, so better to improve municipal sewage treatment plants." – Interviewee 17
Useful for large hospitals: "If you have a big hospital that already has it's own system, then you can say that's the place where very likely you can put in the advanced treatment." – *Interviewee 18*	**PhAC levels in hospital wastewater relatively low:** "No, it's no use at all. This is a common misunderstanding because sewage from hospitals usually contains less pharmaceuticals per litre than sewage from hospitals. And you know why? Because in a hospital, there is usually 10 staff on each patient, that is the average, if you look on a 24 hour basis. And the use of water in a hospital per person is much higher than in a household. So the dilution is more substantial." – *Interviewee 19*
Use of urine separation before treatment: "People in Switzerland from EAWAG… they promote very much urine separation processes in hospitals. Those would be measures that can be applied." – *Interviewee 27*	**Can only be done in new hospitals and only removes 30% of municipal PhAC load:** "Only possible in new constructed facilities and only 30 % of the total load in municipal sewage will be collected." – *Interviewee 20*

Table 5.16. Interviewees' comments on the separate treatment of hospital wastewater.

however, were concerned about the cost of such upgrades. Optimization was also seen as feasible, with a score of 6.9. The low cost of this strategy made it politically palatable, although some interviewees questioned whether it was possible to optimize plants for PhAC removal without reducing the removal of other contaminants (Table 5.15). Separate treatment of hospital wastewater scored somewhat less well in terms of feasibility, at 6.1, largely because of the cost of such treatment (Table 5.16). Both feasibility and effectiveness are important considerations in the selection of management strategies for PhACs.

5.3.6.3 *Perspective of the pharmaceutical industry*

Interviewees who were members of the pharmaceutical industry were asked about the industry's perspective on various management strategies. Their responses suggest that the pharmaceutical industry must not be seen as a uniform body, but as a diverse group, within which there are a variety of views on PhACs in the environment. For instance, Interviewees 24 and 25 were advocates of the concept of 'green' drug development, with Interviewee 25 stating that his company already develops such products. Interviewee 24 commented, "it becomes entirely feasible, when there's a commercial advantage." Interviewee 24 believed that incentives such as patent extensions for companies which produce green drugs, would provide a commercial advantage. Interviewee 22 seemed initially sceptical of the concept, but thought the idea of providing companies with incentives for manufacturing green drugs "sounds like it would be helpful." He questioned, however, the feasibility of using patent extensions in fair manner, without allowing for loopholes. Interviewees 26 and 23 were unreservedly opposed to the idea of developing 'green' drugs, suggesting that the drug development process was too complex to be able to include environmental considerations (Table 5.13). However, Interviewees 22 and 26 pointed out that the pharmaceutical industry does contribute to the protection of the environment by implementing green manufacturing processes, which minimize the use of solvents, and by treating wastewater from the manufacturing process with highly advanced technology.

Because of suggestions by Waterloo Region residents that the pharmaceutical industry should fund management strategies to mitigate environmental contamination by

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PhACs (Ch. 4), interviewees were asked if they thought their companies might contribute to pharmaceutical returns programs, including public education, or to the upgrading of municipal WWTPs. While support for enhancing wastewater treatment in general varied, not surprisingly, none of the interviewees felt the pharmaceutical industry should be asked to contribute to the cost of upgradient municipal WWTPs. Interviewee 22 suggested that it was not clear who should be considered responsible for environmental contamination by PhACs: "While the patients are taking the medicine, who's responsible? Is it us? The doctor who prescribed the medicine? The patient who gets treated by it? So I think it's a much more complex issue." Interviewee 24 was very concerned about the industry being saddled with the cost of upgrading WWTPs: "Frankly this is what I'm afraid of here in the United States, that if the industry doesn't get out front of this issue, then a frustrated legislative body is basically going to pass a law saying, 'you do it.'". The response to pharmaceuticals returns programs was somewhat more positive, with Interviewee 22 suggesting that manufacturers might contribute to such a program, as long as a level playing field was created through legislation (Table 5.11). Interviewees 24 and 26, while not vehemently opposed to returns programs, questioned their effectiveness.

Risk assessment legislation received a relatively positive response from industry interviewees. Interviewee 26 believed that data collection through risk assessment regulations was essential, but emphasized the need for such regulations to be transparent, criticizing the use of assessment factors (safety factors), and universalized, reducing the need for extra experimentation to provide slightly different data in different countries. Interviewee 22 was concerned about the lack of clear risk management outcomes as a result of risk assessment, and expressed a view of risk assessment as purposeless paperwork (Table 5.12). Interviewee 24 was, on one hand, concerned about regulatory action, but felt, on the other hand, that restrictions on registration of environmentally harmful drugs, where better alternatives existed, might lead to the creation of a market for 'green' drugs:

> Environmental impact becomes a significant factor in not only the decision to approve a new medicine, but also in decisions to potentially withdraw existing products because more environmentally friendly and equivalently efficacious

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alternatives exist. The take home message from that becomes the environmental impact of your new pharmaceutical becomes a significant factor in the overall commercial success of that compound, not only in terms of whether or not you're going to register it, but how long you're going to be able to keep in on the market. So that what should happen is companies thinking about discovering and developing new medicines will start to plan from the get-go how to manage the environmental fate of their molecules, in terms of potentially building into the actual chemical scaffold an environmental degratory mechanism, a sensitivity to ultraviolet light, for example.

The interviewee also cited a case where risk assessment led to the registration of an estrogen patch being refused for environmental reasons, because 90% of the active ingredient would remain in the patch after use and environmentally friendly alternates were available. Thus, pharmaceutical industry interviewees were divided in their views of most management strategies, including risk assessment regulations, the manufacturing of 'green' drugs, pharmaceutical returns programs and upgrading wastewater treatment facilities.

5.4 Conclusions

The interviewees had mixed opinions on the science and management of pharmaceuticals in the environment, although some interesting trends and tendencies were observed. Interviewees generally saw PhACs in the environment as both a human health and an ecosystem health concern, although they believed it was more likely that PhACs would have serious or irreversible impacts on aquatic ecosystems than on human health. They ranked pharmaceuticals below some well-known water contaminants such as nutrients, pesticides, and metals, in terms of need for management action, but above localized contaminants such as organic solvents and road salt. European interviewees ranked PhACs higher than North American interviewees, and also tended to favour the use of the precautionary principle in environmental decision making. Interviewees generally saw the uncertainty surrounding the scientific understanding of the impacts of PhACs on aquatic ecosystems as high; they suggested that research to improve the understanding of the ecotoxicology of PhACs should be a priority. According to the

interviewees, governments internationally are conducting research on environmental exposure and effects of PhACs and pollution prevention, but are engaging in little management action other than introducing risk assessment legislation. Although many interviewees said they would like to see risk assessment regulations implemented, they viewed them as ineffective as a means of mitigating the environmental impacts of pharmaceuticals. Advanced wastewater treatment technology, education of medical professionals to reduce over-prescription, and pharmaceutical returns programs coupled with public education, were seen as the most effective management strategies for PhACs. Among these, pharmaceutical returns programs were seen as the most feasible management strategy and received some support from interviewees from the pharmaceutical industry. The views of the interviewees on the nature of the problem of PhACs in the environment, on research needs and on potential management strategies, will be of use in evaluating precautionary options to mitigate the release of PhACs to the environment.

5.5 References

Canadian Standards Association. (1997). *CAN/CSA-Q850-97: Risk management: a guideline for decision-makers*. Etobicoke, ON.

CEPA. (1999). Canadian Environmental Protection Act: The House of Commons of Canada, Bill C-32, as passed by the House of Commons, June 1, 1999.

Commission of the European Communities. (2000). *Communication from the Commission on the precautionary principle* (No. COM (2000)1). Brussels.

CPMP. (2001). *Discussion paper on environmental risk assessment of non-genetically modified organisms (non-GMO) containing medicinal products for human use.* (No. CPMP/SWP/4447/00). London, UK: Committee for Proprietary Medicinal Products.

Datta, L.-e. (1997). A pragmatic basis for mixed-method designs. In V. J. Caracelli (Ed.), *Advances in mixed-method evaluation: the challenges and benefits of integrating diverse paradigms* (Vol. 74, pp. 33-46). San Francisco: Jossey-Bass Publishers.

Doerr-MacEwen, N. A., & Haight, M. E. (2005). Tailoring the precautionary principle to pharmaceuticals in the environment: accounting for experts' concerns. In A. G. Kungolos, C. A. Brebbia & E. Beriatos (Eds.), *Sustainable Development and Planning II* (Vol. 1, pp. 281-291). Southampton: WIT Press.

Doerr-MacEwen, N. A., & Haight, M. E. (2006). Expert stakeholders' views on the management of human pharmaceuticals in the environment. *Environmental Management, 38*, 853-866.

Eckel, W. P., Ross, B., & Isensee, R. K. (1993). Pentobarbital found in ground water. *Ground Water, 31*(5), 801-804.

FDA. (1998, July). *Guidance for industry: Environmental Assessment of human drug and biologics applications*. Retrieved March 4, 2003, from http://www.fda.gov/cder/guidance/index.htm

Foddy, W. (1993). *Constructing questions for interviews and questionnaires: theory and practice in social research*. Cambridge: Cambridge University Press.

Government of British Columbia. (1997). *Waste management act: Post-consumer residual stewardship program regulation. B.C. Reg. 111/97, O.C. 333/97.*

Gray, J. S., & Bewers, J. M. (1996). Towards a scientific definition of the Precautionary Principle. *Marine Pollution Bulletin, 32*(11), 768-771.

Greene, J. C., & Caracelli, V. J. (1997). Defining and describing the paradigm issue in mixed-method evaluation. In V. J. Caracelli (Ed.), *Advances in mixed-method evaluation: the challenges and benefits of integrating diverse paradigms* (Vol. 74, pp. 5-18). San Francisco: Jossey-Bass Publishers.

Greene, J. C., Caracelli, V. J., & Graham, W. F. (1989). Toward a conceptual framework for mixed-method evaluation designs. *Educational Evaluation and Policy Analysis, 11*(3), 255-274.

Health Canada. (2002, November 15 2002). *Health Canada to require environmental asssessments of products regulated under the Food and Drug Act*. Retrieved November 20, 2002, from http://www.hc-sc.gc.ca/english/media/releases/2001.2001_98e.htm

Health Canada. (2005). *Options analysis paper: an environmental assessment regime for new substances in products regulated under the Food and Drugs Act*. Retrieved August 4, 2005, from http://www.hc-sc.gc.ca/ear-ree/ear_options_analysis_e.html#appc

Heberer, T. (2002). Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicology Letters, 131*, 5-17.

Heberer, T., Feldmann, D., Reddersen, K., Altmann, H., & Zimmerman, T. (2002). Production of drinking water from highly contaminated surface waters: Removal of organic, inorganic, and microbial contaminants applying mobile membrane filtration units. *Acta hydrochimica hydrobiologia, 30*, 24-33.

Jobling, S., Nolan, M., Tyler, C. R., Brightly, G., & Sumpter, J. P. (1998). Widespread sexual disruption in wild fish. *Environmental Science and Technology, 32*, 2498-2506.

Krosnick, J. A., & Fabrigar, L. R. (1997). Designing rating scales for effective measurement in surveys. In D. Trewin (Ed.), *Survey measurement and process quality* (pp. 141-164). New York: John Wiley & Sons.

Lissemore, L., Hao, C., Yang, P., Sibley, P. K., Mabury, S., & Solomon, K. R. (2006). An exposure assessment for selected pharmaceuticals within a watershed in Southern Ontario. *Chemosphere, 64*, 717-729.

McColl, S., Hicks, J., Craig, L., & Shortreed, J. H. (2000). *Environmental health risk management: a primer for Canadians*. Waterloo: Network for Environmental Risk Assessment and Management.

McGarvin, M. (2001). Science, precaution, facts and values. In A. Jordan (Ed.), *Reinterpreting the precautionary principle* (pp. 35-60). London: Cameron May.

Morgan, M. G., Pitelka, L. F., & Shevliakova, E. (2001). Elicitation of expert judgments of climate change impacts on forest ecosystems. *Climatic Change, 49*, 279-307.

National Research Council. (1983). *Risk assessment in the federal government: managing the process*. Washington, D.C.: National Academy Press.

O'Connor, D. R. (2002). *Report of the Walkerton inquiry: the events of May 2000 and related issues, Part I*. Toronto: Government of Ontario.

Palys, T. (1997). *Research decisions: quantitative and qualitative perspectives* (2nd ed.). Toronto: Harcourt Canada.

Purdom, C. E., Hardiman, P. A., Bye, V. J., Eno, N. C., Tyler, C. R., & Sumpter, J. R. (1994). Estrogenic effects of effluents from sewage treatment works. *Chemical Ecology, 8*, 275-285.

Rogers, M. D. (2001). Scientific and technological uncertainty, the precautionary principle, scenarios and risk management. *Journal of Risk Research, 4*(1), 1-15.

Sedlak, D. L., & Pinkston, K. E. (2001). Factors affecting the concentrations of pharmaceuticals released to the aquatic environment. *Water Resources Update, 120*, 56-64.

SIGRE. (2002). *Por la salud de la naturaleza: Memoria de actividades* (Pamphlet).

Stan, H. J., Heberer, T., & Linkerhagner, M. (1994). Vorkommen von Clofibrinsaure im aquatischen System -- Fuhrt die therapeutische Anwendung zu einer Belastung von Oberflachen-, Grund- und Trinkwasser? *Vom Vasser, 79*, 57-68.

Steel, B., List, P., Lach, D., & Shindler, B. (2004). The role of scientists in the environmental policy process: a case study from the American west. *Environmental Science & Policy, 7*, 1-13.

Stockholm läns landsting. (2005). *Environmentally classified pharmaceuticals*. Stockholm.

Ternes, T. A. (1998). Occurrence of drugs in German sewage treatment plants and rivers. *Water Research, 32*(11), 3245-3260.

Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M., et al. (2003). Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Research, 37*, 1976-1982.

The Presidential/Congressional Commission on Risk Assessment and Risk Management. (1997). *Framework for environmental health risk management: final report, volume 1*. Retrieved June 2, 2004, from http://www.riskworld.com/Nreports/1997/risk-rpt/pdf/EPAJAN.PDF

United Nations General Assembly. (1992). *Report of the United Nations conference on environment and development* (No. A/CONF.151/26 Vol. I). Rio de Janeiro.

VICH. (2000). *CVMP/VICH Topic GL6 (Ecotoxicity Phase I) Step 7 Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I.* (No. CVMP/VICH/592/98). London, UK: European Agency for the Evaluation of Medicinal Products.

von Krauss, M. P. K., Casman, E. A., & Small, M. J. (2004). Elicitation of expert judgments of uncertainty in the risk assessment of herbicide-tolerant oilseed crops. *Risk Analysis, 24*(6), 1515-1527.

Wiener, J. B., & Rogers, M. D. (2002). Comparing precaution in the United States and Europe. *Journal of Risk Research, 5*(4), 317-349.

Zwiener, C., & Frimmel, F. H. (2000). Oxidative treatment of pharmaceuticals in water. *Water Research, 34*, 1881-1885.

Chapter 6: Analysis of policy strategies for human PhACs in the environment

6.1 Introduction

The ubiquitous presence of human pharmaceuticals in aquatic environments, coupled with concerns about the effects of these substances on ecosystems (possibly including humans), requires that management action to mitigate the release of pharmaceuticals to the environment be evaluated and possibly implemented. As discussed in Chapter 3, under circumstances of scientific uncertainty such as those surrounding PhACs in the environment, the precautionary principle demands that reasonable action be taken to protect the environment. The principle allows for such action to be taken without a quantitative risk assessment; qualitative assessment of risk is sufficient (Commission of the European Communities, 2000; McCarty & Power, 2000). Chapter 2 discussed evidence of risk in the form of findings of PhACs in surface water, groundwater, and drinking water, internationally, as well as in the form of discoveries of subtle, chronic effects of PhACs on aquatic organisms in field and laboratory studies. Chapter 4 furthermore presented evidence that PhACs are entering natural waters in a Canadian municipality; evidence of pharmaceutical contamination of the Canadian environment is supported by other researchers' findings of PhACs in wastewater effluent and in surface water in several Canadian towns and cities (Lee, Sarafin, Peart, & Svoboda, 2004; Metcalfe et al., 2003). Finally, Chapters 4 and 5 presented evidence suggesting that stakeholders are concerned about the presence of pharmaceuticals in the environment and would for the most part be in favour of some form of management action to mitigate environmental contamination by PhACs. On the basis of scientific evidence of the presence and possible effects of PhACs in the environment, stakeholder concerns, and the precautionary principle, it is suggested that the development of management strategies to mitigate the release of PhACs to the environment is needed.

This final chapter involves an analysis of policies to reduce the release of PhACs in general, and more specifically those most likely to have detrimental effects, to the environment, with a predominantly Canadian context. This is the 'decision' component of the risk management framework shown in Chapter 3, Figure 3.2, or the 'options analysis' component of the CSA framework in Chapter 3, Figure 3.1. Much of the

discussion of policies or management strategies is applicable internationally, but in certain circumstances policies appropriate for Canada are not appropriate elsewhere. In particular, legal complications (as reported by several Ch. 5 stakeholders) make returning unused medications to pharmacies in the U.S. very difficult and under-consumption of medications in the Netherlands (as reported by a Ch. 5 stakeholder) makes reducing pharmaceutical consumption less feasible in that country. Some discussion of jurisdictional issues related to the management of PhACs in Canada is included in Section 6.7., but in general jurisdictional issues are beyond the scope of the analysis.

6.2. Methods

Multiple methods for the analysis of policies exist, ranging from traditional, often quantitative forms of analysis, to highly qualitative, post-positivistic forms of analysis (Hanberger, 2001; Linkov et al., 2004). Multi-criteria decision analysis (MCDA) is a popular form of quantitative, mathematical policy analysis, in which stakeholders or decision makers give policies numerical scores according to how they perform on certain criteria, whose weighting allows for the calculation of an optimal policy choice (Belton & Stewart, 2002; Linkov et al., 2004). Such highly mathematical analysis has been criticized, however, for taking a reductionist approach, failing to explore the complexities of policy options, creating a false pretense of objective analysis, and insufficiently including or improperly addressing values and other normative concerns in the analysis (Fischer, 1995; Hanberger, 2001). Qualitative, post-positivistic policy analysis emphasizes the normative, with the view that quantification is neither necessary nor desirable (Hanberger, 2001). However, even post-positivistic, qualitative analysts recognize the value of using the structured framework of rational, quantitative policy analysis, as long as the analysis is not over-simplified by such an approach (Fischer, 1995; Hanberger, 2001). Therefore, the policy analysis method used here is a qualitative approach, based on the rational policy analysis framework presented by Patton and Sawicki (1993), and used in MCDA approaches (Belton & Stewart, 2002; Linkov et al., 2004). It is similar to the methodology used by Barron & Ng (1996) for an analysis of solid waste management strategies in Hong Kong. Because governments usually implement a mixture of policy instruments rather than a single strategy in isolation

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(Barron & Ng, 1996), and as analyses of single policies in isolation have been criticized (Falconer, 1998), the management strategies are combined into policy packages using the feasible manipulations method of May (1981).

6.3 Policy Goals and Objectives

All policies must have broad, overarching goals, as well as more specific objectives. According to Ho (2000), some common goals include justice, economic efficiency, economic growth, and sustainable development. Stone (2002) also describes some widely used, broad policy goals: equity, efficiency, security and liberty. Sustainable development is related to the goals of equity and security; for example, the Bruntland Commission definition emphasizes inter-generational equity: "Sustainable development is development that meets the needs of current generations without compromising the ability of future generations to meet their needs and aspirations." (World Commission on Environment and Development, 1987, p. 43). Sustainable development through pollution prevention, and thereby the protection of the environment and human health from the risks of toxic substances, is the overarching goal of the Canadian Environmental Protection Act (CEPA, 1999). As the policy problem under consideration here also involves finding ways of protecting human and environmental health from potentially detrimental contaminants, and as sustainable development encompasses other goals such as equity, sustainable development is chosen here as the underlying goal for the policy analysis.

Sustainable development is often considered to have 3 main components: environmental health, economic prosperity and social equity (Environment Canada, 1997; Shields, Šolar, & Martin, 2002). Although the focus of this policy analysis is environmental health in particular, economic prosperity and social equity must also be maintained. An ecosystem approach is taken here, meaning that rather than protecting the environment only for the sake of human health and security, the environment must be protected for its own sake. Humans are considered part of ecosystems, rather than separate from or dominating them (Boetzkes & Scott Robert, 2000; Great Lakes Research Advisory Board, 1978; Grumbine, 1994). Thus a less anthropocentric view of sustainability than that described by the Brundtland Commission (above) is taken.

The first policy objective, under the sub-goal of protecting environmental health, is the reduction of the release of PhACs to as low as reasonably practical. The second goal is the reduction of the release of the most harmful PhACs to the environment. Although it may seem logical that this second objective should be the main objective, the difficulty in determining which PhACs are likely to have detrimental effects, as discussed in Chapter 2, makes this objective problematic. Furthermore, rather than effects-based management, exposure-based management, which aims to reduce all contamination as much as possible, is becoming the norm in environmentally conscious European countries such as Sweden (Falconer, 1998); and pollution prevention in general is one of Environment Canada's main principles for sustainable development (Environment Canada, 1997). For these reasons the first and main objective involves minimizing the release of all PhACs to the environment, rather than focusing exclusively on the most harmful PhACs.

6.4. Policy Criteria

An essential component of policy analysis is the evaluation of policies against pre-determined criteria (Patton & Sawicki, 1993). Some of these criteria are specific to the problem at hand, and are meant, for example, to measure the degree to which policies are likely to meet objectives. Others, such as financial cost, are important considerations in the evaluation of most policies. Table 6.1 presents criteria used to evaluate policies, a) in a general context, by Patton and Sawicki (1993); b) in a solid waste management context, by Barron and Ng (1996); and c) in a pesticide management context, by Falconer (1998). The criteria selected for use in this analysis are also shown.

Four criteria are common to studies by Patton & Sawicki (1993), Barron & Ng (1996), and Falconer (1998), and they are also to be applied in this study: cost, effectiveness, feasibility, and equity considerations. The economic ramifications of implementing a policy are essential at any level of decision making, and for all decision makers, whether individuals, businesses, or governments, because of the opportunity costs of implementing such policies. Implementing an expensive policy means fewer resources will be available for other policy initiatives. Effectiveness is essentially a measure of whether a policy meets its objectives; an ineffective policy is a failed policy.

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Patton & Sawicki (1993)	Barron & Ng (1996)	Falconer (1998)	This Study
Cost	Least Financial Cost	Cost	Minimal Financial Cost
Benefit			Increase in Environmental Stewardship/Awareness
			Benefit to environmental quality at large
Effectiveness	Perception of Effectiveness	Dependability in Meeting Environmental Goals	Effectiveness in: 1) Reduction of PhAC loading to environment, 2) Reduction of loading of most harmful PhACs to environment
Risk	Ecological Impacts		Minimal increase in other environmental or health risks
Political Viability	Ease of Implementation	Permanence of Policies	Feasibility
Administrative Ease		Administrative Practicality	
Legality			(Screening)
Uncertainty			
Equity	Equity Considerations	Compatibility with Distributional/ Ethical Concerns	(Screening)
Timing			
	Compliance Monitoring/ Enforcement		Compliance Monitoring/Enforcement
	Robustness/ Flexibility	Adaptability of Policy Framework	Adaptability/ Flexibility
	Macroeconomic Impacts		
	Economic Efficiency		
		Ability to Implement Controls on Differential Basis	Selectivity

Table 6.1. Policy criteria suggested by Patton & Sawicki (1993), Barron & Ng (1996), and Falconer (1998), and used in this study.

Therefore effectiveness is a vital criterion. Feasibility, including political viability and administrative ease, is key to the success of a policy in practice. A policy which appears effective in theory, but which would be politically damaging to implement, or which faces administrative barriers, is unlikely to ever be put into practice. Finally, equity is an ethical criterion which all policymakers strive to meet, and an important policy goal. Ho (2000) suggests that broad policy criteria like equity, which are also goals, should be treated as constraints, unlike more specific criteria such as cost, which can be treated as maximands. Therefore the criterion of equity, and also the criterion of legality, will be treated as screening criteria in this analysis; any policy package which appears to be inequitable or illegal will not be considered for further evaluation.

Other criteria to be considered in this analysis include the benefit of increasing environmental quality in general; minimally increasing other risks (especially other environmental or health risks); capacity to monitor compliance with the policy; adaptability and flexibility of the policy; and selectivity, the ability to target specific locations or specific products with the policy. Minimally increasing other risks is important as policies cannot be considered in isolation, nor can environmental compartments; a policy which reduces the release of PhACs to the environment but increases the release of other contaminants is sub-optimal. A policy which benefits environmental quality beyond reducing PhAC release, should receive extra consideration for its added benefits. Environmental quality can be improved directly, for instance by mitigating the release of other contaminants to water; or indirectly, by enhancing environmental stewardship and awareness, which should lead to a long-term improvement in environmental quality. The capacity to monitor policy compliance and effectiveness is important because of the iterative and adaptive nature of the risk management process. Information on the performance of policies is needed so adjustments can be made where compliance and effectiveness are insufficient. Policies themselves must also be flexible, so they can be adapted as new information is acquired; flexibility is essential given the high degree of uncertainty associated with the issue of PhACs in the environment (see Chapter 3). Finally, it is also advantageous to have policies which can be targeted geographically, temporally, or which can selectively

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address particular products, addressing aspects of the PhAC issue such as localized contamination, or pharmaceutical-specific concerns.

6.5. Policy Packages: Feasible Manipulations

A wide variety of policy instruments, meeting the criteria of equity and legality, and to some degree the other criteria discussed above, are available for the management of PhACs in the environment. Table 6.2 describes the manipulation of these policy variables to different degrees (low, medium, and high), according to the methods of May (1981). May (1981) suggests that different policy variables, or instruments, can be applied to differing degrees, and that it is by combining the policy instruments, applied at different strengths, into policy packages, that the best overall policy approaches emerge. The policy variables and the meaning of the degrees of manipulation are discussed below. In Table 6.3, the policy variables are combined into several sets of policy strategies, in accordance with the methodology of May (1981).

The first policy variable is environmental risk assessment regulations. Such regulations are currently the only policy in place internationally that address the environmental impacts of PhACs. The U.S. has existing regulations requiring environmental assessments for human pharmaceuticals (FDA, 1998), while the EU has draft guidelines for the assessment (CHMP, 2005), and Canada is currently in the process of developing environmental assessment regulations (Health Canada, 2002). As discussed in Chapter 5, while most stakeholders are in favour of such regulations, they question their effectiveness, given the limited capacity of current risk assessment methods to detect the complex effects of PhACs. Furthermore, there remains much debate concerning what the outcome of the environmental assessment should be. Should the environmental assessment regulation merely ensure the development of a database on the environmental impacts of PhACs? Should PhACs be labelled based on their environmental risks, to the degree to which these can be determined, as is being considered in Sweden (Stockholm läns landsting, 2005)? Should the prohibition of registration, in other words, the banning of pharmaceuticals because of environmental concerns, be an option? These three possibilities are presented as the 'low, moderate, and high' degrees of manipulation of the variable of environmental assessment regulation.

Variables	Low	Moderate	High
Environmental Assessment Regulations	Regulations requiring submission on data pertaining to environmental impacts for PhACs; information gathering only, not tied to any management outcome	Regulations requiring submission on data pertaining to environmental impacts for PhACs, with labelling of any PhACs of concern	Regulations requiring submission on data pertaining to environmental impacts for PhACs, with labelling of any PhACs of concern, and the possibility of banning PhACs of special concern
Pharmaceutical Returns Programs	Encourage pharmacies and pharmaceutical industry to voluntarily set up returns programs for proper drug disposal, and to make consumers aware of the programs	Regulations requiring the pharmaceutical industry to implement returns programs and to conduct some advertising to make consumers aware of the programs	Regulations requiring the pharmaceutical industry to implement returns programs and to conduct large-scale public awareness and education campaigns regarding the environmental impacts of PhACs
Education of Medical Practitioners and Patients to Reduce Pharmaceutical Use	Small-scale education campaign to make physicians aware of the need to reduce drug use for environmental reasons	Medium-scale education campaign to made physicians aware of the need to reduce drug use for environmental reasons, pointing out pharmaceuticals of particular concern	Large-scale education campaign to made physicians and the public aware of the need to reduce drug use for environmental reasons, suggesting that certain pharmaceuticals be used as a last resort only
Green drug Manufacturing	Encourage pharmaceutical manufacturers to voluntarily produce 'green' drugs, allowing market force to create a demand	Extend patents on 'green' pharmaceuticals to encourage manufacturers to produce them	Financial incentives to the pharmaceutical industry for the production of 'green' drugs
Municipal Wastewater Treatment	Optimize existing WWTPs to better remove PhACs without upgrading	Fund upgrading all WWTPs in cities where effluent makes up 10% or more stream flow	Fund upgrading WWTPs in large cities or areas of high PhAC contamination to include advanced treatment methods such as ozonation
Hospital Wastewater Treatment	Status quo: special treatment for hospital wastewater not required	Fund largest hospitals to pre-treat their wastewater using secondary treatment before release to municipal systems	Fund all hospitals to pre-treat their wastewater using secondary treatment before release to municipal systems

Table 6.2. Feasible manipulation of policy variables for the management of PhACs in the environment to low, moderate, and high degrees, according to the methods of May (1981).

Pharmaceutical returns programs can reduce the entry of pharmaceuticals into the environment through proper disposal. Although disposal is believed to be a minor contributor to environmental contamination in comparison with the release of PhACs through consumption and excretion (Heberer, Feldmann, Reddersen, Altmann, & Zimmerman, 2002), some estimates suggest that up to a third of pharmaceuticals may be disposed of rather than used (Greiner & Rönnefahrt, 2003). Furthermore, pharmaceutical returns programs were one of the preferred options of stakeholders in Chapter 5. Currently, the Model Standardsof Practice for Canadian Pharmacists state that pharmacists should collect medications for proper disposal, and proper disposal of medications is being incorporated into provincial professional codes of ethics in most Canadian provinces. In European countries and Canadian provinces, the pharmaceutical sectors (including manufactuers, pharmacies, etc.), together with governments, voluntarily organize returns programs for pharmaceuticals (NAPRA, 2002; SIGRE, 2002). Some examples include Nova Scotia's 'Dead Drugs' program and PEI's 'Take it Back' programs (Halasi, 2005). Such voluntary systems are the basis of the 'low' degree of manipulation shown in Table 6.2. Chapter 4, together with research by Health Canada (COMPAS for Health Canada, 2002), suggest, however, that many Canadians continue to dispose of their pharmaceuticals improperly, throwing them in the toilet or in the garbage. Furthermore, the National Association of Pharmacy Regulatory Agencies (NAPRA) believes that increased public awareness through promotion, and more organized and convenient returns programs, together with increased funding from stakeholders, are needed (Halasi, 2005). Therefore, a stronger approach to the variable of pharmaceutical returns may be needed. In the province of British Columbia, waste management regulations require the pharmaceutical industry to organize and advertise for pharmaceutical returns programs (Government of British Columbia, 1997, 2004). Such regulations are described under the 'moderate' level of manipulation in Table 6.4. However, to ensure the public becomes truly aware of the issue of pharmaceuticals in the environment and participate actively in returns programs, education and awareness campaigns on a larger scale than those required by the B.C. regulations may be needed. Regulations requiring the pharmaceutical industry to set up returns program and to carry

out large-scale advertising campaigns, comprise the 'high' level of manipulation of this variable.

Education of medical practitioners and patients to reduce pharmaceutical over-use also emphasizes awareness as a means of reducing environmental contamination by PhACs. Because most PhACs enter the environment after being consumed, reducing unnecessary pharmaceutical consumption is a logical, front-end approach to the problem, and was suggested by several stakeholders in Chapter 5. Furthermore, physicians can be discouraged from collecting large quantities of drug samples.   In 2001, physicians were asked to return unused and expired medications for incineration and proper disposal to Lions Gate hospital in North Vancouver; over a 2-day period, 47 kg of medications were contributed by 25 people; worth $20 000 or more wholesale (Halasi, 2005). Clearly, the disposal of physician samples contributes to the loading of PhACs to the environment. The education of medical practitioners and patients can range from, at the low end, small-scale campaigns to make physicians aware that pharmaceuticals enter and may impact the environment. At a moderate level of manipulation, it entails a somewhat larger campaign, targeting specific pharmaceuticals of concern. For example, physicians might be asked to reduce their prescription of the highly persistent pharmaceutical, carbamazepine (Andreozzi, Raffaele, & Nicklas, 2003; Clara, Strenn, & Kreuzinger, 2004; Cordy et al., 2004), or of antibiotics commonly found in environmental samples. Returns programs for physicians, such as the case discussed above, in Vancouver, would be implemented. The high level of manipulation would involve a campaign targeting not only medical practitioners but also the public, and would suggest that pharmaceuticals such as carbamazepine be used only as a last resort. Additionally, alternatives to the use of physician drug samples would be sought; trial prescription programs, allowing patients to pick up small quantities of medications for free from pharmacies, rather than from physicians' collection, could provide such alternatives (Halasi, 2005).

The manufacture of environmentally friendly pharmaceuticals, or 'green' drugs, which degrade quickly, and have little to no effect on non-target organisms, is in theory an ideal approach to the management of PhACs in the environment. If such drugs can be manufactured, the environmental issue is dealt with up front, and management strategies later in the product lifecycle become less necessary. Daughton (2001; 2003a; 2003b)

believes that green pharmaceutical manufacturing is essential and perhaps the most important strategy for the management of PhACs in the environment, but his ideas are the subject of much controversy among scientists, managers, and members of the pharmaceutical industry (see Ch. 5). Furthermore, the question must be asked as to how pharmaceutical manufacturers can be convinced to put research efforts into the development of 'green' drugs. Some members of the industry feel that market forces alone provide incentive for companies to develop a niche market in the manufacture of 'green' drugs (Ch. 5). This is the basis of the 'low' level of manipulation of the 'green' pharmaceutical manufacturing variable. However, further inducements may be needed to convince the industry to invest in green manufacturing; such inducements are an increasingly common policy instrument in the management of environmental contaminants. One suggestion by an industry stakeholder in Chapter 5 was to provide extensions on patents for 'green' pharmaceuticals. This constitutes the moderate level of manipulation. A final option, at the 'high' level of manipulation, would be to provide financial incentives, such as tax breaks, to companies which manufacture 'green' pharmaceuticals.

Municipal wastewater treatment technology has been the subject of much discussion in the academic literature, as a means of reducing the release of PhACs to the environment. Because most PhACs pass through wastewater treatment plants (WWTPs) before entering the environment, removal of PhACs by WWTPs has the potential to strongly reduce environmental contamination. Some researchers believe upgrading WWTPs is the best way of managing PhACs in the environment (O'Brien & Dietrich, 2004). Certainly, scientific research indicates that advanced treatment methods such as ozonation and membrane filtration effectively remove PhACs from the water (Heberer et al., 2002; Huber, Canonica, Park, & Von Gunten, 2003; Ternes et al., 2003; Zwiener & Frimmel, 2000). But the degree of upgrading can vary. At a low level, optimization of existing WWTPs to better remove PhACs, without upgrading the WWTP technology, is an option. A moderate level of manipulation might involve upgrading all WWTPs in cities with where effluent is 10% or more of streamflow to a minimum of secondary treatment. As reported by the Sierra Legal Defense Fund (2004), some large Canadian municipalities such as Montreal and Halifax release their wastewater without treatment;

others such as Charlottetown employ only primary treatment. While much of this wastewater is released to oceans, some is released to inland rivers and streams; 15% of inland municipalities still do not have secondary wastewater treatment. Therefore the upgrades entailed in the 'moderate' level of manipulation could contribute to reducing the release of PhACs to the environment. Finally, a high level of manipulation would entail upgrading WWTPs in large municipalities, and in areas where PhAC concentrations in surface water are relatively high, to include advanced wastewater treatment methods such as ozonation. Based on Chapter 4, Section 4.5.3, ozonation appears to be more financially viable than membrane filtration at this time.

Hospital wastewater treatment is a technical variable similar to municipal wastewater treatment. Hospital wastewater may contain certain pharmaceuticals, such as antineoplastics (chemotherapy drugs) and antimicrobials, at levels higher than municipal wastewater (Al-Ahmad, Daschner, & Kümmerer, 1999; Kümmerer, Steger-Hartmann, & Meyer, 1997; Steger-Hartmann, Kümmerer, & Hartmann, 1997). In some cases the concentrations of antibiotics in hospital wastewater have been found to be near the MIC_{50} values for pathogenic bacteria; concentrations at which the development of antimicrobial resistance may occur (Kümmerer, Al-Ahmad, & Mersch-Sundermann, 2000; Kümmerer & Henninger, 2003). Not only do PhACs enter hospital wastewater by excretion, but hospital staff are permitted to dispose of small quantities of non-narcotic, non-neoplastic pharmaceuticals via the toilet (Canadian Society of Hospital Pharmacists (CSHP), 1997). Currently, in Canada, hospitals are not required to pre-treat wastewater before releasing it to municipal systems; the status quo is considered the 'low' level of manipulation of this variable. At a moderate level of manipulation, large hospitals only could be required to treat wastewater with secondary methods before releasing it to municipal sewage collection systems. And at a high level of manipulation, all hospitals could be required to treat their wastewater before releasing it to municipal systems.

These variables, manipulated to different degrees, can be combined to form policy packages, or alternative policy strategies. Table 6.3 illustrates the strategies which will be considered for analysis. The first strategy, called 'minimalism', involves little effort to manage PhACs in the environment, beyond some data collection through risk

	Minimalism	Incrementalism	Moderation	Command & Control	Front End	Education & Awareness	Stakeholder Effective	Local Efforts
Environmental Assessment Regulations	L	M	M	H	M	M	L	L
Pharmaceutical Returns Programs	L	M	M	M	M	H	M	M
Education of Medical Practitioners and Patients to Reduce Pharmaceutical Use	L	L	M	L	M	H	H	L
Green drug manufacturing	L	L	M	L	H	L	L	L
Municipal wastewater treatment	L	M	M	L	L	L	H	H
Hospital wastewater treatment	L	L	M	L	L	L	M	L

Table 6.3. Combination of policy variables into policy packages or strategies, according to the methods of May (1981). The letters L, M, and H refer to low, medium, and high; the degrees of manipulation of each variable as shown in Table 6.2.

assessment regulations, some minor efforts at education, and encouragement of voluntary risk management action on the part of the pharmaceutical industry. The next strategy, called 'incrementalism', involves some active management, through the potential labelling of environmentally harmful PhACs, the development of regulations related to pharmaceutical returns programs, and upgrades to primary treatment for those municipalities without such treatment. While this does not constitute an overwhelming effort to keep PhACs out of natural waters, Hrudey (1996) believes that incrementalism is the best way of managing uncertain environmental risks such as the PhAC issue. Incrementalism is also among the most adaptive approaches to policy making and management (see Ch. 3). The third strategy, called 'moderation', involves a moderate level of manipulation of all variables;such a moderate approach could potentially reduce the release of PhACs to the environment while remaining affordable and feasible. The remaining policy packages involve particular approaches to the management of PhACs in the environment. One such approach is the 'command and control' strategy, where environmental risk assessment regulations are paramount, and regulations for pharmaceutical returns programs are also included. The 'front-end' strategy takes a green manufacturing approach while trying to minimize the entry of pharmaceuticals into the waste stream. 'Education and awareness' focuses on teaching the public and physicians about the environmental risks of pharmaceuticals. The 'stakeholder effective' package emphasizes those management strategies deemed most effective by stakeholders in Chapter 5. Finally, the 'local efforts' package emphasizes management which can occur on a local scale; advanced wastewater treatment in cities which need it most, and local pharmaceutical returns programs, regulated, however, by a higher level of government.

6.6 Policy Evaluation

The policy strategies are evaluated by means of comparison against the criteria discussed in section 6.4. Table 6.4 presents a qualitative scoring of strategies against evaluation criteria. It should be kept in mind that not all criteria are equally important; the criteria of effectiveness, feasibility, and cost, are the most vital criteria, whereas the remaining criteria, while still of interest, are somewhat less crucial.

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Criteria	Minimalism	Incrementalism	Moderation
Effectiveness in: 1) Reduction of PhAC loading to environment, 2) Reduction of loading of most harmful PhACs to environment	**P** – Will have little effect on release of PhACs	**S** – Mandatory pharmaceutical returns programs and secondary WWTPs in all cities will reduce PhAC loading somewhat, and labelling resulting from EA regulations will reduce the release of the most harmful PhACs. But many PhACs will still be released.	**VG** – By targeting the issue from many angles, a significant reduction in PhAC release should be achievable, although this reduction will be incomplete without advanced wastewater treatment
Feasibility	**E** – Easiest strategy to implement	**E** – Incrementalism corresponds closely with what stakeholders in Ch. 5 deemed most feasible.	**VG** – Generally feasible although patent extensions for drug companies and separate wastewater treatment for hospitals somewhat less so
Minimal Financial Cost	**E** – Least expensive	**VG** – The main expense is the upgrading of WWTPs to secondary treatment. This will be expensive but not unreasonably so.	**S** – Costs of upgrading municipal WWTPs and funding wastewater treatment in large hospitals may be somewhat prohibitive
Minimal increase in other environmental or health risks	**E** – Little is being done so little effect in increasing other risks	**VG** – Upgrading WWTP treatment facilities may slightly increase energy use and therefore CO_2 emissions.	**S** – Upgrading municipal WWTPs and requiring hospital wastewater treatment will increase energy use
Benefit to environmental quality at large	**P** – No direct benefits to environmental quality and little awareness/stewardship	**VG** – Upgrading WWTPs will improve river and stream quality generally, and required pharmaceutical returns programs will enhance awareness/stewardship	**E** – Upgrading WWTPs and installing hospital wastewater treatment will enhance surface water quality, and education of physicians and returns programs will enhance awareness
Adaptability/ Flexibility	**E** – Not locked into any long-term strategies	**VG** – WWTP upgrades are somewhat inflexible but overall the incremental strategy allows for adaptation	**S** – Although education-related strategies are flexible, wastewater treatment related strategies are not
Compliance Monitoring/Enforcement	**P** – Voluntary strategies difficult to monitor	**S** – Regulatory control on returns programs allows for some compliance monitoring, as does funding for WWTP upgrades. Labelling of PhACs resulting from environmental assessments does not result in behaviour that can be monitored.	**S** – Regulated variables and funded technological upgrades can be monitored but education of physicians, labelling, and particularly outcomes of patent extensions from green drugs are hard to monitor
Selectivity	**P** – No targeting of local contamination or harmful PhACs	**S** – WWTP upgrades are not targeted but labelling of PhACs targets compounds of greatest concern	**LS** – This strategy does not target any aspect of the PhAC problem, or any geographic location, although some PhACs are targeted

Table 6.4a. Evaluation for strategies, 'minimalism', 'incrementalism', and 'moderation'.

E=Excellent, VG=Very Good, S=Satisfactory, LS=Less than Satisfactory, P=Poor.

Criteria	Command & Control	Front End	Education & Awareness
Effectiveness in: 1) Reduction of PhAC loading to environment, 2) Reduction of loading of most harmful PhACs to environment	**LS** – EA regulations may result in banning of some harmful PhACs but will miss others, and returns programs will have a minor impact	**VG** – Should be effective in theory but in practice, perhaps less so	**VG** – If consumption and improper disposal are reduced, could be quite effective. But effectiveness of education campaigns always questionable.
Feasibility	**S** – Ethical considerations and political viability of banning pharmaceuticals needed for health	**LS** – Stakeholder in Ch. 5 did not consider 'green' manufacturing feasible	**VG** – Pharmaceutical industry might object but otherwise feasible
Minimal Financial Cost	**E** – Not financially expensive	**P** – Cost of providing incentives large enough to influence drug companies huge!	**S** – Large-scale education campaigns are expensive
Minimal increase in other environmental or health risks	**S** – No effects on environmental risks but banning drugs could increase health risks	**E** – Should not increase other risks	**VG** – No increase in environmental risks but possible health risk if patients refuse to take medication because of environmental concern
Benefit to environmental quality at large	**S** – Some increase in environmental awareness though returns programs and labelling	**VG** – Benefit in terms of environmental awareness	**VG** – Definite benefit in terms of awareness
Adaptability/ Flexibility	**VG** – Regulations can be amended	**VG** – Incentives can be modified, as can education programs	**E** – Education campaigns easy to modify
Compliance Monitoring/Enforcement	**E** – Command & control allows for enforcement	**P** – Difficult to monitor effects of incentive for green drugs and of education	**LS** – Can regulate returns programs but effects of education hard to monitor
Selectivity	**S** – Selective for PhACs but not for location	**S** – Would replace most harmful PhACs but not geographically selective	**S** – Targets certain PhACs but not geographically selective

Table 6.4b. Evaluation for strategies, 'command & control', 'front end', and 'education & awareness'. E=Excellent, VG=Very Good, S=Satisfactory, LS=Less than Satisfactory, P=Poor

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Criteria	Stakeholder Effective	Local Efforts
Effectiveness in: 1) Reduction of PhAC loading to environment, 2) Reduction of loading of most harmful PhACs to environment	**E** – This package deemed highly effective by stakeholders in Ch. 5	**E** – Advanced wastewater treatment highly effective
Feasibility	**S** – High level of technological requirements plus large scale education campaign may harm feasibility	**VG** – Generally feasible despite large technological investment because targeted at certain municipalities
Minimal Financial Cost	**LS** – Cost of advanced WWTPs, large education campaign, and of hospital wastewater treatment relatively high	**S** – Advanced wastewater treatment expensive but not prohibitively so because applied selectively
Minimal increase in other environmental or health risks	**LS** – Energy intensive advanced treatment increases release of CO_2. Also ozonation generates reaction products of unknown effect.	**LS** – Energy intensive advanced treatment increases release of CO_2. Also ozonation generates reaction products of unknown effect.
Benefit to environmental quality at large	**VG** – Better wastewater treatment benefits rivers and streams; education increases awareness	**VG** – Better wastewater treatment benefits rivers and streams; education increases awareness
Adaptability/ Flexibility	**LS** – Heavy investments in technology not easy to modify but education programs more easily modified	**LS** – Heavy investments in technology not easy to modify but returns programs more easily modified
Compliance Monitoring/Enforcement	**S** – Technological component can be monitored but education component less so	**VG** – Technological component easy to monitor, regulated returns programs can be somewhat monitored
Selectivity	**E** – Advanced technology geographically targeted and education targets certain PhACs	**VG** – Geographically targeted but not targeted at particular PhACs

Table 6.4c. Evaluation for strategies, 'stakeholder effective' and 'local efforts'

E=Excellent, VG=Very Good, S=Satisfactory, LS=Less than Satisfactory, P=Poor

Only two of the policy strategies received the lowest possible score, 'poor', on one of the three main criteria. The strategy of 'minimalism' received this score for effectiveness; as the strategy entails little action beyond the status quo, it is not expected to significantly reduce the release of PhACs to the environment. Performing poorly on the criterion of effectiveness means that this policy strategy would not meet the objectives outlined in Section 6.3. Therefore this strategy should not be considered for implementation. The strategy, 'front end', which relies heavily upon incentives to induce the pharmaceutical industry to produce 'green' drugs, received a poor score in terms of financial cost. Providing financial incentives sufficiently large to influence the pharmaceutical industry would be extremely expensive, to the point of being prohibitive. PRMA (Pharmaceutical Researchers and Manufacturers of America, 2003) estimate that the research costs to bring 1 drug to market over a 10 year period are $700 million CDN. Assuming that an incentive of at least 10% of the costs of drug development would be needed to influence the industry, a 70 million dollar (CDN) investment would be required over 10 years as an incentive for the manufacturing of a single 'green' drug. Furthermore, stakeholders were not convinced of the feasibility of green manufacturing; while some stated that green manufacturing is already occurring, others considered the concept, "naïve" (Ch. 5). Although the 'front end' strategy scored well in terms of criteria including effectiveness, minimal increase in other environmental risks, benefit to environmental quality at large, and adaptability, its poor performance in terms of cost and feasibility suggests that this strategy should not be implemented at this time. While green manufacturing has the potential, in theory, to effectively reduce the environmental impacts of PhACs, it will likely be up to pharmaceutical companies to develop their own niche markets in this area, without the help of government incentives or policies.

Two strategies received scores of less than satisfactory for one main criterion, and satisfactory for another. 'Command & Control', which emphasized environmental assessment regulations, including labelling and banning as outcomes, as well as regulated pharmaceutical returns programs, was deemed unlikely to be highly effective. As discussed in Ch.2 and Ch. 5, and in the academic literature, risk assessment methodology is insufficient for the detection of the subtle, detrimental impacts resulting from the pharmacological activity of PhACs, and mixture effects add complexity to the difficulties

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of risk assessment (Länge & Dietrich, 2002; O'Brien & Dietrich, 2004; Sanderson et al., 2004). Therefore, few substances are likely to be prohibited from entering the market due to such regulations. Furthermore, it is not clear whether such regulations would address the large number of substances already on the market, which might also have environmental impacts. Pharmaceutical returns programs, while beneficial, and while being ranked highly in terms of effectiveness by stakeholders, can only prevent a fraction of PhACs from entering the environment; among the largest estimates is 1/3 of pharmaceuticals (Greiner & Rönnefahrt, 2003). Another important consideration is the feasibility of banning pharmaceuticals due to their environmental impacts. Because most pharmaceuticals are needed for the maintenance of patient's quality of life, banning them is arguably unethical; one can argue that doing so violates the patients' autonomy, treating the patient as a means to the end of environmental protection, rather than as an end in themselves (Paton, 1958). This policy has the benefits, however, of being relatively inexpensive, adaptable, and enforceable. Nevertheless, because of the problems with effectiveness, feasibility, and ethical issues in particular, this is not one of the best policy packages available.

The 'stakeholder effective' package, designed to be highly effective, scored less well in terms of feasibility and financial cost. The strategy includes a high level of manipulation on both municipal wastewater treatment and education of physicians, as these were the two strategies considered most effective by stakeholders. Pharmaceutical returns programs and hospital wastewater treatment are manipulated to a moderate degree, as they were also considered relatively effective strategies. Putting large efforts into various forms of technological improvement and some large-scale education campaigns, however, may harm feasibility, and certainly results in a high cost for this strategy. For example, the Region of Waterloo spends $110 000 per year on education campaigns regarding waste management (pers. comm.., Deanna Dakin, Regional Municipality of Waterloo); extrapolating this to a national scale, an investment of approximately $8 million CDN might be needed for a large-scale education campaign. In terms of advanced wastewater treatment, in Chapter 4, it is estimated that installing and operating ozonation would cost slightly less than $10 CDN per resident per year in a mid to large sized city. Assuming 10% of the Canadian population lives in a municipality

requiring advanced treatment, with the country's population being approximately 25 million, a cost of 25 million dollars would be required for the upgrades. This figure does not include the extra cost of installing wastewater treatment systems in large hospitals. Therefore the total cost of this strategy would be over $35 million CDN. The cost is large although not necessarily prohibitively so, given the benefits; the strategy performs well in terms of benefiting the environment at large, by generally improving surface water quality and by increasing environmental stewardship and awareness. The use of advanced wastewater treatment in large cities or areas with high PhAC concentrations also makes the strategy selective. However the adaptability is limited, compliance monitoring is somewhat difficult for the education campaigns, and the energy used for advanced municipal wastewater treatment and hospital wastewater treatment will increase the release of CO_2 to the atmosphere. This strategy is not optimal at the present time, but it should be kept in mind for the future. If it becomes increasingly clear, through the acquisition of more scientific evidence, that PhACs are harmful to the environment, it may be worthwhile investing in expensive and somewhat inflexible strategies to mitigate their release.

The strategy, 'education & awareness', performed well in terms of benefit to environmental quality at large, by making people aware of the impact of their actions on the environment; it is also extremely flexible, feasible, and should not increase risks to the environment or health, unless patients become afraid of taking medications seen as bad for the environment. The strategy could be quite effective in theory, because it aims to reduce both consumption of pharmaceuticals and improper disposal, though education. However, the success of education campaigns is questionable. While campaigns encouraging people to recycle have been relatively successful, with 70-80% of Ontarians participating in blue-box programs by 1991 (Alberni Environmental Coalition, 1991), campaigns encouraging people to reduce energy consumption and thereby CO_2 emissions, do not appear to have met with much success in Canada, as greenhouse gas emissions have generally increased over the past decade (David Suzuki Foundation, 2005). Furthermore, as a stakeholder in Ch. 5 suggested, there is pressure from the pharmaceutical industry, and from patients, for physicians to prescribe drugs. Finally, many of the pharmaceuticals consumed are necessary for quality of life; therefore it is not

possible to reduce their consumption. So although returns programs and physician/public education were ranked quite highly in terms of effectiveness by stakeholders, it is argued that only a moderate level of effectiveness can be expected from this strategy. Furthermore, the large-scale education campaigns that would be required to achieve even a moderate level of success, would likely be expensive, as discussed with regard to the 'stakeholder effective' strategy. While the 'education & awareness' strategy should not be rejected entirely, other policy packages which rely only partially, rather than entirely, on education campaigns, may be more effective.

The three remaining strategies have in common, at a minimum, a moderate level of manipulation of the variables of municipal wastewater treatment and pharmaceutical returns programs. They are, in order of increasing effectiveness, 'incrementalism', 'moderation', and 'local efforts'. However 'moderation' and 'local efforts' are more expensive and less feasible than 'incrementalism'. Selecting a preferred strategy among these three is difficult, although 'incrementalism' and 'local efforts' appear slightly better than 'moderation'; if the most important point is effectiveness (as this researcher suggests it ideally should be), 'local efforts' appears best. However, if the purpose is simply to achieve some small reduction in PhAC loading, with the maintenance of low cost and high feasibility being essential (which may be more realistic), 'incrementalism' seems best. Looking beyond the criteria of effectiveness, feasibility, and cost, 'incrementalism' performs well as upgrading WWTPs to secondary treatment improves water quality, without consuming the quantities of energy that would be required if hospitals also treated their wastewater ('moderation'), or if advanced wastewater treatment methods were used ('local efforts'). Furthermore, the 'incrementalism' strategy is reasonably adaptive, not making overly heavy or immutable commitments. 'Local efforts', however, also performs reasonably well on secondary criteria, as it can be monitored, is highly geographically targeted, and should also increase stream and river quality. 'Moderation' performs only slightly less well. Based on the qualitative scoring of the strategies, they can be ranked in different ways, depending on whether effectiveness, cost and feasibility, or secondary criteria, are used to separate strategies which perform similarly well (Table 6.5.). It is suggested therefore, that particularly among the top 3 strategies, the choice of which strategy should be left up to the decision maker; no single, optimal strategy will be

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selected here. Furthermore, other strategies such as 'stakeholder effective', which performed only moderately well overall, should be kept in mind for the future, as new information is certain to affect the evaluation of the policy packages.

Ranking	Effectiveness	Cost & Feasibility	Secondary Criteria
1	Local Efforts	Incrementalism	Incrementalism
2	Moderation	Local Efforts,	Local Efforts
3	Incrementalism	Moderation	Moderation
4	Education & Awareness	Education & Awareness	Education & Awareness
5	Stakeholder Effective	Command & Control	Command & Control
6	Command & Control	Stakeholder Effective	Stakeholder Effective
7	Front End	Minimalism	Front End
8	Minimalism	Front End	Minimalism

Table 6.5. Rankings of policy strategies, depending on whether effectiveness, cost and feasibility, or secondary criteria are used to distinguish between similarly-performing strategies.

6.7. Jurisdictional issues within Canada

This analysis has been conducted without considering which level of government might be responsible for implementing the different policy strategies. In fact, most of the strategies suggested would require a mixture of efforts on the part of federal, provincial, and local governments. The federal government is responsible for environmental assessment regulations; these will be administered either by Health Canada or Environment Canada (Health Canada, 2002). Regulations regarding pharmaceuticals returns programs appear to fall under provincial jurisdiction; British Columbia has included pharmaceutical returns programs under its waste management regulations, specifically its regulations on recycling (Government of British Columbia, 1997, 2004). However, all governments have the ability to influence their citizens' participation in returns programs through education and awareness campaigns. Local governments may

be particularly influential in the education process; for instance, the Region of Waterloo distributes a monthly environmental newsletter, which could potentially include information on returning unused or expired medications to the pharmacy. Similarly, various levels of government could implement the education of medical practitioners and patients to reduce pharmaceutical over-consumption. It might be most practical, however, to conduct such education at a federal or provincial level, through cooperation with an association of medical practitioners such as the College of Family Physicians of Canada or the Natinal Pharmacy Regulatory Agency (NAPRA). Any attempts to influence pharmaceutical manufacturers to produce green drugs – whether through patent extensions, or financial incentives such as tax breaks – would likely have to occur at a federal level; provincial and particularly municipal governments would have difficulty influencing such large and powerful corporations. The installation of advanced systems in municipal WWTPs, or the upgrading of WWTPs to secondary treatment, would occur on a local scale. However municipal governments are unlikely to have sufficient funds for such upgrades; grants from provincial and federal governments would be needed. Similar grants would be needed for the installation of wastewater treatment facilities at hospitals. In essence, while local governments have an important role to play with respect to education and awareness regarding PhACs in the environment, much of the financial and regulatory burden in managing this issue would need to be carried by federal and provincial governments for the policy strategies to be implemented.

6.8. Conclusions

The precautionary principle requires that policy strategies be developed to manage human pharmaceuticals in the environment. The overarching goal of these policies would be sustainable development, with environmental protection as a sub-goal. More specifically, the objectives of such policies would be to minimize the release of PhACs in general, as well as particular PhACs of concern, to the environment. Strategies to manage PhACs in the environment must be equitable and legal. It is important that they be effective, feasible, and of minimal cost; furthermore they should have additional benefit in terms of generally improving environmental quality, and should not generate increased risk to the environment or human health; they should be adaptive, selective, and

enforceable. In this analysis, several policy variables, including risk assessment regulations, pharmaceutical returns programs, education of medical practitioners, incentives for 'green' pharmaceutical manufacturing, municipal wastewater treatment and hospital wastewater treatment, were combined to form different policy packages. Among these packages, 'local action', 'incrementalism', and 'moderation' appeared to be the best strategies. 'Local action' involves upgrading the WWTPs of large municipalities or those with high downstream PhAC concentrations to include advanced treatment, as well as some regulations and education related to pharmaceutical returns programs. 'Incrementalism' also involves regulated returns programs, as well as risk assessment regulations with environmental labelling of pharmaceuticals as an outcome, and the upgrading of WWTPs in cities of 10 000 or more to secondary treatment, where such treatment is not already in place. Finally, 'moderation', involved a moderate degree of action on all the variables discussed above. Municipal, provincial, and federal governments will need to collaborate in implementing such strategies to mitigate the environmental impacts of human pharmaceuticals.

6.9. References

Al-Ahmad, A., Daschner, F. D., & Kümmerer, K. (1999). Biodegradability of cefotiam, ciprofloxacin, meropenem, penicillin G., and sulfamethoxazole and inhibition of waste water bacteria. *Archives of Environmental Contamination and Toxicology, 37*(158-163).

Alberni Environmental Coalition. (1991). *Recycling in Canada*. Retrieved October 10, 2005, from http://www.portaec.net/library/recycling/recycling_in_canada.html

Andreozzi, R., Raffaele, M., & Nicklas, P. (2003). Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environments. *Chemosphere, 50*, 1319-1330.

Barron, W. F., & Ng, G. T. L. (1996). An assessment methodology for environmental policy instruments: an illustrative application to solid wastes in Hong Kong. *Journal of Environmental Management, 48*, 283-298.

Belton, V., & Stewart, T. J. (2002). *Multiple criteria decision analysis: an integrated approach*. Boston: Kluwer Academic Publishers.

Boetzkes, E. A., & Scott Robert, J. (2000). Toward an inclusive health ethic for humans and ecosystems. *Ethics and the Environment, 5*(2), 143-151.

Canadian Society of Hospital Pharmacists (CSHP). (1997). *Guideline for handling and disposal of hazardous pharmaceuticals (including cytotoxic drugs)*. Ottawa, ON.

CEPA. (1999). Canadian Environmental Protection Act: The House of Commons of Canada, Bill C-32, as passed by the House of Commons, June 1, 1999.

CHMP. (2005). *Guideline on the environmental risk assessment of medicinal products for human use (draft)*. London: European Medicines Agency (EMEA).

Clara, M., Strenn, B., & Kreuzinger, N. (2004). Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behavior of carbamazepine in wastewater treatment and during groundwater infiltration. *Water Research, 38*, 947-954.

Commission of the European Communities. (2000). *Communication from the Comission on the precautionary principle* (No. COM (2000)1). Brussels.

COMPAS for Health Canada. (2002, November 6). *F&DA environmental assessment regulations project benchmark survey: a report to Health Canada (POR-02-13) Office of Regulatory and International Affairs*. Retrieved February 25, 2004, from http://www.hc-sc.gc.ca/ear-ree/fda_report_entire_e.html#executive

Cordy, G. E., Duran, N. L., Bower, H., Rice, R. C., Furlong, E. T., Zaugg, S. D., et al. (2004). Do pharmaceuticals, pathogens, and other organic waste water compounds persist when waste water is used for recharge? *Ground Water Monitoring and Remediation, 24*(2), 58-69.

Daughton, C. G. (2001). Pharmaceuticals and personal care products in the environment: Overarching issues and overview. In C. G. Daughton & T. L. Jones-Lepp (Eds.), *Pharmaceuticals and personal care products in the environment: Scientific and regulatory issues* (pp. 2-38). Washington: American Chemical Society.

Daughton, C. G. (2002). Environmental stewardship and drugs as pollutants. *The Lancet, 360*, 1035-1036.

Daughton, C. G. (2003a). Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health -- Part 1: Rationale and avenues toward a green pharmacy. *Environmental Health Perspectives, 111*, 757-774.

Daughton, C. G. (2003b, March 19-21). *Environmental stewardship of pharmaceuticals: the green pharmacy.* Paper presented at the 3rd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, Minneapolis, MN.

David Suzuki Foundation. (2005). *All over the map: a comparison of provincial climate change plans*. Retrieved October 10, 2005, from http://www.davidsuzuki.org/files/climate/Ontario/All_Over_the_Map.pdf

Environment Canada. (1997). *Environment Canada's sustainable development strategy 1997-2000*. Retrieved September 23, 2005, from http://www.ec.gc.ca/sd-dd_consult/final/SDGTOC_E.HTM

Falconer, K. E. (1998). Managing diffuse environmental contamination from agricultural pesticides: An economic perspective on issues and policy options, with particular reference to Europe. *Agriculture, Ecosystems and Environment, 69*, 37-54.

FDA. (1998, July). *Guidance for industry: Environmental Assessment of human drug and biologics applications*. Retrieved March 4, 2003, from http://www.fda.gov/cder/guidance/index.htm

Fischer, F. (1995). *Evaluating public policy*. Chicago: Nelson-Hall Publishers.

Government of British Columbia. (1997). *Waste management act: Post-consumer residual stewardship program regulation. B.C. Reg. 111/97, O.C. 333/97.*

Government of British Columbia. (2004). *Recycling Regulation*. Retrieved September 22, 2005, from http://wlapwww.gov.bc.ca/epd/epdpa/ips/pdf/recycling_regulation.pdf

Great Lakes Research Advisory Board. (1978). *The ecosystem approach: scope and implications of an ecosystem approach to transboundary problems in the Great Lakes Basin* (special report). Windsor, ON: International Joint Commission.

Greiner, P., & Rönnefahrt, I. (2003, April 14-16). *Management of environmental risks in the life cycle of pharmaceuticals.* Paper presented at the Envirapharma, Lyon.

Grumbine, E. R. (1994). What is ecosystem management? *Conservation Biology, 8*(1), 27-38.

Halasi, S. (2005). Waste not, want not: a guide to appropriate disposal of used, expired or unwanted drugs. *Pharmacy Practice, 21*(10), 34-41.

Hanberger, A. (2001). What is the policy problem? Methodological challenges in policy evaluation. *Evaluation, 7*(1), 45-62.

Health Canada. (2002, November 15 2002). *Health Canada to require environmental asssessments of products regulated under the Food and Drug Act*. Retrieved November 20, 2002, from http://www.hc-sc.gc.ca/english/media/releases/2001.2001_98e.htm

Heberer, T., Feldmann, D., Reddersen, K., Altmann, H., & Zimmerman, T. (2002). Production of drinking water from highly contaminated surface waters: Removal of organic, inorganic, and microbial contaminants applying mobile membrane filtration units. *Acta hydrochimica hydrobiologia, 30*, 24-33.

Ho, L. S. (2000). The nature of optimal public policy. *International Journal of Social Economics, 27*(7/8/9/10), 1013-1019.

Hrudey, S. E. (1996). A critical review of current issues in risk assessment and risk management. In J. H. Shortreed (Ed.), *Technical risk issues in business and regulatory decision-making* (pp. 17-31). Waterloo: Institute for Risk Research.

Huber, M. M., Canonica, S., Park, G.-Y., & Von Gunten, U. (2003). Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environmental Science and Technology, 37*(5), 2003.

Kümmerer, K., Al-Ahmad, A., & Mersch-Sundermann, V. (2000). Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test. *Chemosphere, 40*, 701-710.

Kümmerer, K., & Henninger, A. (2003). Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clinical Microbiology and Infection, 9*, 1203-1214.

Kümmerer, K., Steger-Hartmann, T., & Meyer, M. (1997). Biodegradability of the anti-tumor agent ifosfamide and its occurrence in hospital effluents and communal sewage. *Water Research, 31*(11), 2705-2710.

Länge, R., & Dietrich, D. (2002). Environmental risk assessment of pharmaceutical drug substances -- conceptual considerations. *Toxicology Letters, 131*, 97-104.

Lee, H.-B., Sarafin, K., Peart, T. E., & Svoboda, M. L. (2004). Acidic pharmaceuticals in sewage -- methodology, stability test, occurrence, and removal from Ontario samples. *Water Quality Research Journal of Canada, 38*(4), 667-682.

Linkov, I., Varghese, A., Jamil, S., Seager, T. P., Kiker, G., & Bridges, T. (2004). Multi-criteria decision analysis: a framework for structuring remedial decisions at contaminated sites. In A. Ramadan (Ed.), *Comparative risk assessment and environmental decision making* (pp. 15-54). Amsterdam: Kluwer.

May, P. J. (1981). Hints for crafting alternative policies. *Policy Analysis, 7*, 227-244.

McCarty, L. S., & Power, M. (2000). Approaches to developing risk management objectives: an analysis of international strategies. *Environmental Science & Policy, 3*, 311-319.

Metcalfe, C. D., Koenig, B. G., Bennie, D. T., Servos, M., Ternes, T. A., & Hirsch, R. (2003). Occurrence of neutral and acidic drugs in the effluents of Canadian

sewage treatment plants. *Environmental Toxicology and Chemistry, 22*(12), 2872-2880.

NAPRA. (2002). *Recycling and disposal of dispensed drugs*. Retrieved February 9, 2003, from http://www.napra.org/docs/0/97/194/184.asp

O'Brien, E., & Dietrich, D. R. (2004). Hindsight rather than foresight: reality versus the EU draft guideline on pharmaceuticals in the environment. *TRENDS in Biotechnology, 22*(7), 326-330.

Paton, H. J. (1958). *The categorical imperative: A study in Kant's moral philosophy*. London: Hutchinson & Co.

Patton, C. V., & Sawicki, D. S. (1993). *Basic methods of policy analysis and planning* (2nd ed.). Upper Saddle River: Prentice-Hall.

Pharmaceutical Researchers and Manufacturers of America. (2003). *Why do medicines cost so much?* Retrieved March 12, 2003, from http://www.phrma.org/publications/brochure/questions/whycostmuch.cfm

Sanderson, H., Johnson, D. J., Reitsma, T., Brain, R. A., Wilson, C. J., & Solomon, K. R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology, 39*, 158-183.

Shields, D. J., Šolar, S. V., & Martin, W. E. (2002). The role of values and objectives in communicating indicators of sustainability. *Ecological Indicators, 2*, 149-160.

Sierra Legal Defense Fund. (2004). *The national sewage report card (number 3): grading the sewage treatment of 22 Canadian cities* (No. ISBN 0-9733213-3-4).

SIGRE. (2002). *Por la salud de la naturaleza: Memoria de actividades* (Pamphlet).

Steger-Hartmann, T., Kümmerer, K., & Hartmann, A. (1997). Biological degradation of cyclophosphamide and its occurrence in sewage water. *Ecotoxicology and Environmental Safety, 36*, 174-179.

Stockholm läns landsting. (2005). *Environmentally classified pharmaceuticals*. Stockholm.

Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M., et al. (2003). Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Research, 37*, 1976-1982.

World Commission on Environment and Development. (1987). *Our common future*.

Oxford and New York: Oxford University Press.

Zwiener, C., & Frimmel, F. H. (2000). Oxidative treatment of pharmaceuticals in water.

Water Research, 34, 1881-1885.

Ch. 7: Conclusions

7.1 Conclusions

After a decade of research consistently indicating the presence of pharmaceuticals in natural waters, it is time that management action to reduce their release to the environment be considered. Such management action must be based, firstly, on current scientific understanding of the issue. A review of the literature suggests that human PhACs are entering the environment primarily through consumption, followed by excretion, entry into the wastewater collection system, and treatment at wastewater treatment plants; as many PhACs are not effectively removed during secondary treatment, they are subsequently released to surface waters (Heberer, 2002a). Advanced treatment methods such as ozonation, membrane filtration, and activated carbon, can, however, remove PhACs more effectively (Adams, Wang, Loftin, & Meyer, 2002; Boyd, Reemtsma, Grimm, & Mitra, 2003; Heberer, Feldmann, Reddersen, Altmann, & Zimmerman, 2002; Huber, Canonica, Park, & Von Gunten, 2003; Ternes et al., 2003; Zwiener & Frimmel, 2000). Other sources and routes of entry for human PhACs include disposal to toilet and landfill (Eckel, Ross, & Isensee, 1993; Greiner & Rönnefahrt, 2003; Holm, Rugger, Bjerg, & Christensen, 1995); spreading of sewage sludge on agricultural land followed by runoff (Lissemore, Yang, Hao, & Solomon, 2005); industrial release of PhACs, particularly in manufacturing wastewater (Balcýoðlu & Ötker, 2003; Guardabassi, Petersen, Olsen, & Dalsgaard, 1998); and the washing off of dermally applied PhACs during bathing and swimming (Daughton & Ternes, 1999). Human PhACs are frequently detected in surface water; less commonly in groundwater; and only a handful of PhACs have been detected in drinking water (Heberer, 2002a, 2002b; Ternes, 1998). Their presence raises concerns about possible impacts on aquatic ecosystems and human health. Field and laboratory evidence of the effects of low concentrations of PhACs on aquatic organisms exists; some well-known examples include the feminization of fish exposed to 17α-ethinylestradiol (Jobling, Nolan, Tyler, Brightly, & Sumpter, 1998; Larsson et al., 1999; Purdom et al., 1994), and the spawning of mussels exposed to the antidepressant fluoxetine (Fong, 1998). Human health risk assessments suggest that PhAC concentrations in drinking water may be too low to

present a risk (Christensen, 1998; Schulman et al., 2002; Webb, Ternes, Gibert, & Olejniczak, 2003); however the effects of long-term exposure to mixtures of PhACs, as well as effects on sensitive sub-populations, cannot be ruled out (Daughton & Ternes, 1999). The possibility of mixture effects, and the complex nature of the mechanisms through which pharmaceuticals affect organisms, make the effects of PhACs, particularly on non-target species, very difficult to predict, leading to gaps in understanding (Brain et al., 2004; Länge & Dietrich, 2002). However, certain classes of PhACs are believed to be of particular concern; these include antimicrobials; synthetic hormones; lipid regulators; anti-inflammatories and analgesics; antiepileptics; and selective serotonin reuptake inhibitors. Furthermore, based on data available in the literature, it was possible to conduct a rough, back-of-the envelop ranking of pharmaceuticals according to expected environmental risk (Table 2.3). This ranking suggests that the PhACs carbamazepine, clofibric acid, ifosfamid, 17α-ethinylestradiol, oxytetracycline, ciprofloxacin, and diclofenac, may be of particular concern. Nevertheless, uncertainty in the scientific understanding of PhACs in the environment remains high.

Risk management provides an appropriate framework for addressing the issue of human PhACs in the environment. However, problems are encountered at the scientific risk assessment stage of risk management, as the methodology to quantitatively assess the risks of PhACs, particularly to aquatic organisms, has not been fully developed. This inability to quantitatively assess risk could potentially stall the risk management process; however the precautionary principle provides an impetus for risk management to continue despite incomplete science, as it states that uncertainty must not be used as a reason for postponing risk management and for allowing environmental damage to continue (CEPA, 1999; Commission of the European Communities, 2000; Government of Canada, 2001; Quijano, 2003). The theory of adaptive planning is also of use in coping with uncertainty, as it suggests that environmental policies developed under conditions of uncertainty must have characteristics such as flexibility, to allow them to respond to evolving scientific understanding (Holling, 1978; Lessard, 1998). By applying the precautionary principle and the theory of adaptive planning to the U.S. EPA risk management framework (The Presidential/Congressional Commission on Risk

Assessment and Risk Management, 1997a, 1997b), a modified risk management framework particularly suited to PhACs in the environment was developed (Ch. 3).

Based on this framework, a study of potential PhAC management strategies at a local scale, in the Region of Waterloo, was conducted. Analysis of wastewater indicated that PhACs were indeed being released from local WWTPs at concentrations similar to those in other urban areas. The precautionary principle therefore suggests that management action is desirable. Questionnaires administered locally suggested that many people dispose of their medications improperly, and that education programs might therefore be of help in reducing the release of PhACs to the environment. Local residents were interested in seeing management action taken, but their willingness to pay for such management action was limited. Installing ozonation equipment to remove PhACs from wastewater, did, however, fall within the range of what residents were willing to pay. It is therefore recommended that the Region consider both education programs to improve proper pharmaceutical disposal and ozonation of wastewater as future means of minimizing the release of human PhACs to the local environment.

In order to develop management strategies at a broader scale, interviews were conducted with stakeholders from the pharmaceutical industry, government and academia, in Canada, the U.S. and Europe. The stakeholders generally felt that PhACs in the environment represented both an ecosystem and a human health concern, although they thought serious and irreversible impacts on ecosystems were more likely. Contamination of groundwater and surface water by PhACs was seen as less of a concern than contamination by nutrients, pesticides and metals, but a greater concern than contamination by road salt or organic solvents. Interestingly, North American interviewees were more concerned about water contamination by pathogens than by pharmaceuticals, but the reverse was the case for Europeans. The interviewees felt that ecotoxicological research into PhACs in the environment was needed to reduce scientific uncertainty, which they perceived as high. In terms of management, they suggested that governments are doing little at this time to address PhACs other than research. While they supported research activity, many interviewees also felt management action was required. The interviewees liked the idea of risk assessment regulations; however, they saw them as ineffective in mitigating environmental impacts by PhACs. Advanced

wastewater treatment, education of medical professionals, and pharmaceutical returns programs coupled with public education, were considered most likely to effectively prevent environmental impacts by PhACs. Of these three, pharmaceutical returns programs were seen as most feasible, and were favoured to the greatest degree by interviewees from the pharmaceutical industry. These stakeholder consultations may be helpful to governments in developing policies to manage PhACs in the environment.

With the purpose of developing policy recommendations for the management of human PhACs in Canada, a structured policy analysis was conducted. Policy packages were assembled by considering the policy instruments discussed with stakeholders in Ch. 5; the instruments were combined into packages using the feasible manipulations methods of May (1981). Policy strategies were evaluated based on the criteria of effectiveness, feasibility, minimal financial cost, minimal increase in other environmental or health risks, benefit to environmental quality at large, adaptability, potential for compliance monitoring and enforcement, and selectivity. The analysis suggested that the optimal policies involved local efforts, or incremental or moderate application of a variety of policy instruments. A combination of returns programs, education, wastewater treatment and to a lesser degree, green drug development and environmental assessment regulation, was best. Policy packages focusing excessively on regulation or on incentives for the development of green drugs performed less well, because they were, in the case of the former, ineffective, and in the case of the latter, overly expensive without necessarily being effective. It is recommended that Canada's federal government consider a combination of strategies to address human PhACs in the environment, rather than focusing solely on risk assessment regulations. WWTP upgrades, together with better returns programs and education, should become part of the government's strategy for managing PhACs in the environment.

In addition to making a practical contribution to the management of PhACs in Canada, this study also provides new insight at a more theoretical level. Pharmaceuticals represent one of many uncertain environmental risks that managers and policy makers are struggling to address. The precautionary principle provides a tool for risk management under conditions of uncertainty, yet it is unclear how the principle should be applied (Ch. 5, Section 3.5). This study on PhACs in the environment can be used as an example of

the application of the precautionary principle in environmental management. The steps followed in developing management strategies can be condensed into a framework for precautionary decision making, shown in Fig. 7.1. The framework shows that precautionary action is needed when there is some evidence of harm, but quantitative risk assessment is not possible. Furthermore, it illustrates that precautionary management action should only be undertaken if it meets stakeholder needs and several criteria including effectiveness and financial affordability. This framework can provide guidance to environmental researchers, managers and policy managers faced with the challenge of uncertain risks, such as the risks posed by PhACs.

Should precautionary management action be undertaken?

```
┌─────────────────────────────────────┐
│  Is there some scientific evidence   │
│  suggesting a risk to human health   │────── no
│  or the environment?                 │
└─────────────────────────────────────┘                    ┌──────────────────┐
                  │                                         │  No need for     │
                 yes                                        │  precautionary   │
                  │                                         │  management      │
                  │                                         │  action          │
          ┌───────────────────────┐                        └──────────────────┘
          │  Is there sufficient   │
   yes ───│  knowledge and data    │
          │  for a thorough,       │
          │  quantitative risk     │
          │  assessment?           │
          └───────────────────────┘
  ┌──────────────────────┐    │
  │ Perform a quantitative│   no
  │ risk assessment – no  │    │
  │ need for the          │    │
  │ precautionary         │    │
  │ principle             │    │
  └──────────────────────┘    │
                    ┌─────────────────────────────┐
                    │ Conduct qualitative risk     │
                    │ assessment and stakeholder   │
                    │ consultation                 │
                    └─────────────────────────────┘
```

-Do stakeholders, including the public, desire management action?
-Do management strategies exist which meet the following criteria (see Ch. 6):
  - effective
  - feasible
  - financially affordable
  - adaptive/flexible
  - benefit environment
  - minimally harm environment/human health
  - increase environmental stewardship
  - enforceable
  - can be applied selectively

yes → Select precautionary management option(s)

no → Precautionary management action may not be desirable

Figure 7.1. A decision-making framework for the application of the precautionary
principle to uncertain environmental risks.

7.2 References

Adams, C., Wang, Y., Loftin, K., & Meyer, M. (2002). Removal of antibiotics from surface and distilled water in conventional water treatment process. *Journal of Environmental Engineering, 128*(3), 253-260.

Balcýoðlu, I. ý. A., & Ötker, M. (2003). Treatment of pharmaceutical wastewater containing antibiotics by O_3 and O_3/H_2O_2 processes. *Chemosphere, 50*, 85-95.

Boyd, G. R., Reemtsma, H., Grimm, D. A., & Mitra, S. (2003). Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *The Science of the Total Environment, 311*, 135-149.

Brain, R. A., Johnson, D. J., Richards, S. M., Hanson, M. L., Sanderson, H., Lam, M. W., et al. (2004). Microcosm evaluation of the effects of an eight pharmaceutical mixture to the aquatic macrophytes *Lemna gibba* and *Myriophyllum sibiricum*. *Aquatic Toxicology, 70*, 23-40.

CEPA. (1999). Canadian Environmental Protection Act: The House of Commons of Canada, Bill C-32, as passed by the House of Commons, June 1, 1999.

Christensen, F. M. (1998). Pharmaceuticals in the environment -- a human risk? *Regulatory Toxicology and Pharmacology, 28*, 212-221.

Commission of the European Communities. (2000). *Communication from the Comission on the precautionary principle* (No. COM (2000)1). Brussels.

Daughton, C. G., & Ternes, T. A. (1999). Pharmaceuticals and personal care products in the environment: Agents of subtle change? *Environmental Health Perspectives, 107*, 907-938.

Eckel, W. P., Ross, B., & Isensee, R. K. (1993). Pentobarbital found in ground water. *Ground Water, 31*(5), 801-804.

Fong, P. P. (1998). Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. *Biology Bulletin, 194*, 143-149.

Government of Canada. (2001). *A Canadian perspective on the precautionary approach/principle: discussion document*. Retrieved May 10, 2004, from http://www.ec.gc.ca/econom/discussion_e.htm

Greiner, P., & Rönnefahrt, I. (2003, April 14-16). *Management of environmental risks in the life cycle of pharmaceuticals.* Paper presented at the Envirapharma, Lyon.

Guardabassi, L., Petersen, A., Olsen, J. E., & Dalsgaard, A. (1998). Antibiotic resistance in acinetobacter spp. isolated from sewers receiving waste effluent from a hospital and a pharmaceutical plant. *Applied and Environmental Microbiology, 64*(9), 3499-3502.

Heberer, T. (2002a). Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicology Letters, 131*, 5-17.

Heberer, T. (2002b). Tracking persistent pharmaceutical residues from municipal sewage to drinking water. *Journal of Hydrology, 266*, 175-189.

Heberer, T., Feldmann, D., Reddersen, K., Altmann, H., & Zimmerman, T. (2002). Production of drinking water from highly contaminated surface waters: Removal of organic, inorganic, and microbial contaminants applying mobile membrane filtration units. *Acta hydrochimica hydrobiologia, 30*, 24-33.

Holling, C. S. (1978). *Adaptive environmental assessment and management*. Chichester: John Wiley & Sons.

Holm, J. V., Rugger, K., Bjerg, P. L., & Christensen, T. H. (1995). Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grinsted, Denmark). *Environmental Science and Technology, 29*(5), 1415-1420.

Huber, M. M., Canonica, S., Park, G.-Y., & Von Gunten, U. (2003). Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environmental Science and Technology, 37*(5), 2003.

Jobling, S., Nolan, M., Tyler, C. R., Brightly, G., & Sumpter, J. P. (1998). Widespread sexual disruption in wild fish. *Environmental Science and Technology, 32*, 2498-2506.

Länge, R., & Dietrich, D. (2002). Environmental risk assessment of pharmaceutical drug substances -- conceptual considerations. *Toxicology Letters, 131*, 97-104.

Larsson, D. G. J., Adolfsson-Erici, M., Parkkonen, J., Pettersson, M., Berg, A. H., Olsson, P.-E., et al. (1999). Ethinyloestradiol -- an undesired fish contraceptive? *Aquatic Toxicology, 45*, 91-97.

Lessard, G. (1998). An adaptive approach to planning and decision-making. *Landscape and Urban Planning, 40*, 81-87.

Lissemore, L., Yang, P., Hao, C., & Solomon, K. (2005). *Are veterinary pharmaceuticals finding their way into Ontario watersheds? An exposure assessment of pharmaceuticals in surface waters within a model watershed in Ontario.* Paper presented at the Source water protection: 12th annual international conference on the St. Lawrence River/Great Lakes Ecosystem, Cornwall, ON.

May, P. J. (1981). Hints for crafting alternative policies. *Policy Analysis, 7*, 227-244.

Purdom, C. E., Hardiman, P. A., Bye, V. J., Eno, N. C., Tyler, C. R., & Sumpter, J. R. (1994). Estrogenic effects of effluents from sewage treatment works. *Chemical Ecology, 8*, 275-285.

Quijano, R. F. (2003). Elements of the precautionary principle. In J. A. Tickner (Ed.), *Precaution, environmental science, and preventive public policy* (pp. 21-27). Washington: Island Press.

Schulman, L. J., Sargent, E. V., Naumann, B. D., Faria, E. C., Dolan, D. G., & Wargo, J. P. (2002). A human health risk assessment of pharmaceuticals in the aquatic environment. *Human and Ecological Risk Assessment, 8*(4), 657-680.

Ternes, T. A. (1998). Occurrence of drugs in German sewage treatment plants and rivers. *Water Research, 32*(11), 3245-3260.

Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M., et al. (2003). Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Research, 37*, 1976-1982.

The Presidential/Congressional Commission on Risk Assessment and Risk Management. (1997a). *Framework for environmental health risk management: final report, volume 1*. Retrieved June 2, 2004, from http://www.riskworld.com/Nreports/1997/risk-rpt/pdf/EPAJAN.PDF

The Presidential/Congressional Commission on Risk Assessment and Risk Management. (1997b). *Risk assessment and risk management in regulatory decision making:*

final report, volume 2. Retrieved June 2, 2004, from

http://www.riskworld.com/Nreports/1997/risk-rpt/volume2/pdf/v2epa.PDF

Webb, S., Ternes, T. A., Gibert, M., & Olejniczak, K. (2003). Indirect human exposure to

pharmaceuticals via drinking water. *Toxicology Letters, 142*, 157-167.

Zwiener, C., & Frimmel, F. H. (2000). Oxidative treatment of pharmaceuticals in water.

Water Research, 34, 1881-1885.

Appendix A: Instrumental parameters for analysis of pharmaceuticals in wastewater (As reported to the Region of Waterloo by C. Metcalfe and X. Miao, 2004)

1. Neutral Drugs

Neutral drugs were analyzed by LC-MS/MS using the APCI source. The column employed was Genesis C18 (150 × 3 mm, 4µ), with a flow rate of 0.5mL/min. The mobile phase consisted of 10mM ammonium acetate aqueous solution (A) and acetonitrile (B). The injection volume was 20 µL. The neutral drugs were separated using the following linear gradient elution profile at room temperature: mobile phase B was increased from the initial 5% to 20% over 4 min and reached 95% at 12 min; it remained at 95% for the next 3 min and then ramped back to 5% within 2 min. Using the software Analyst 1.4., multiple reaction monitoring (MRM) with unit resolution on both of the first and second analyzer was selected for data acquisition in the positive-ion mode and nitrogen was used as curtain, nebulizer, auxiliary and collision gas. The mass spectrometric parameters were optimized by continuously infusing the analytes using a syringe pump at 20µL/min. The syringe pump was then teed into the LC flow of 50:50 10mM ammonium acetate-acetonitrile at 0.5mL/min and determined as follows: curtain gas 20 psi, nebulizer gas 70 psi, auxiliary gas 15 psi, corona discharge needle current 2.0 µA, probe temperature 470°C, interface heater on, CAD gas 5. Collision energy and declustering potential for each compound are listed in the table below. The dwell time for each MRM transition was set at 200 ms.

Compound	MRM	Retention Time (min)	Declustering Potential (V)	Collision Energy (eV)
Caffeine	195 > 138	7.45	47	25
Carbamazepine	237 > 194	10.91	40	28
Cotinine	177 > 80	7.11	40	40
Cyclophosphamide	261 > 140	9.93	40	28
Pentoxifylline	279 > 181	9.09	40	24
Fluoxetine	310 > 148	12.48	15	12
Trimethoprim	291 > 230	8.96	40	28

2. Acidic Drugs

For the acidic drugs, Negative-ion TurboIonSpray source was used. Therefore, a Genesis C18 column of 150×2.1mm, 4µ was employed at the flow rate of 0.2mL/min for the analyses. The mobile phases A and B consisted of 10 mM ammonium acetate aqueous solution and 40:60 acetonitrile-methanol, respectively. The linear gradient elution was performed to separate the analyzed compounds. The initial condition was 20% B which was held for 0.5 min. The mobile phase B was then increased to 40% at 1 min, reached 95% at 9 min and held at this level for 7 min. Next, it was ramped back to 20% over 2 min. The injection volume was 25 µL and the chromatographic separation was conducted at room temperature. By continuously introducing the analytes through a syringe pump at 10µL/min, which was then teed into the LC flow consisting of mobile phases A and B (50:50) at 0.2mL/min, the following mass spectrometric parameters were optimized to achieve reasonable sensitivity for each individual compound operating in multiple reaction monitoring (MRM) mode: curtain gas 30 psi, nebulizer gas 30 psi, turbo gas 60 psi, ionspray voltage –3000 V, heater gas temperature 350°C, interface heater on, CAD gas 5; declustering potential and collision energy were also determined. Nitrogen was used for all kinds of gases and a dwell time of 200 ms was selected for each MRM transition.

Compound	MRM	Retention Time (min)	Declustering Potential (V)	Collision Energy (eV)
Bezafibrate	360 > 274	11.86	–56	–20
Clofibric Acid	213 > 127	10.75	–40	–21
Diclofenac	294 > 250	12.99	–43	–17
Fenoprofen	241 > 197	12.41	–45	–13
Gemfibrozil	249 > 121	15.47	–45	–25
Ibuprofen	205 > 161	13.38	–40	–15
Indomethacin	356 > 312	13.33	–53	–15
Ketoprofen	253 > 209	11.34	–43	–15
Naproxen	229 > 170	11.38	–45	–20

3. Sulfonamides

Six sulfonamide compounds were analyzed using APCI in the positive-ion mode. The separation was conducted on a Genesis C18 column (150 × 3 mm 4 μ) at the flow rate of 0.5mL/min using a linear gradient elution. The mobile phases A and B were water containing 0.1% formic acid and acetonitrile, respectively. The mobile phase B was initially held at 3% for 0.5 min, increased to 24% at 1 min, then further increased to 43% at 10 min and held at 43% for 2 min. Finally, it reached 95% at 13 min and was held for 3 min. Afterwards, B was ramped back to 3% at 17 min. The injection volume was 20 μL and the chromatographic separation was performed at room temperature. Multiple reaction monitoring (MRM) was employed for acquiring mass spectrometric data and two pairs of MRM transitions were selected for each compound. By introducing the analytes through a syringe pump at 20 μL/min which was combined with a LC flow of the mobile phase A and B (50:50) at 0.5mL/min into the mass spectrometer, the optimized operating parameters were determined as follows: curtain gas 15 psi, nebulizer gas 60 psi, auxiliary gas 15 psi, corona discharge needle current 2 μA, probe temperature 450°C, interface heater on, CAD gas 5. Declustering potential and collision energy were also optimized for each compound. Nitrogen was used for the gases of all purposes and a dwell time of 200 ms was set for each MRM transition.

Compound	MRM	Retention Time (min)	Declustering Potential (V)	Collision Energy (eV)
Sulacetamide	215 > 156	5.54	15	20
	215 > 92		15	30
Sulfapyridine	250 > 156	5.90	30	20
	250 > 108		30	40
Sulfadiazine	251 > 156	5.70	30	20
	251 > 108		30	30
Sulfamethoxazole	254 > 156	8.87	30	20
	254 > 108		15	30
Sulfisoxazole	268 > 156	9.31	15	20
	268 > 113		30	20
Sulfamethazine	279 > 186	6.56	30	20
	279 > 124		30	30

4. Fluoroquinolones

The detection of fluoroquinolones was performed with TurboIonSpray source in the positive-ion mode. The chromatography was achieved on a Genesis C18 column (150 × 2.1 mm, 4 μ) with the following linear gradient elution at room temperature, where the mobile phase A was 20 mM ammonium acetate aqueous solution containing 0.1% formic acid and the mobile phase B was acetonitrile: the gradient was increased from 12% to 55% B in 8 min, to 95% in 2 min, then held for 4 min at 95% B and finally ramped back to initial 12% B in 2 min. The flow rate was 0.2mL/min and the injection volume was 20 μL. The mass spectrometer was operated in multiple reaction monitoring (MRM) mode and the corresponding parameters were optimized by introducing fluoroquinolones through a syringe pump at 10 μL/min which was then combined with a LC flow of mobile phases A and B (50:50) at 0.2 mL/min into the mass spectrometer: curtain gas 30 psi, nebulizer gas 30 psi, turbo gas 60 psi, ionspray voltage 1700 V, heater gas temperature 360°C, interface heater on, CAD gas 5. Declustering potential and collision energy were also optimized and characteristic of each individual analyte. Nitrogen was used as curtain, nebulizer, turbo and collision gas. A dwell time of 200 ms was selected for each MRM transition.

Compound	MRM	Retention Time (min)	Declustering Potential (V)	Collision Energy (eV)
Ciprofloxacin	332 > 314	10.44	50	30
Norfloxacin	320 > 302	10.27	50	25
Ofloxacin	362 > 318	10.29	50	30

Appendix B: PhAC concentrations in wastewater and blanks, showing standard deviations, and detection limits.

Table 1. Concentrations of pharmaceutical analytes in wastewater (showing standard deviations) and blanks.

Compound	Kitchener Effluent	Kitchener Influent	Foxboro G. Effluent	Foxboro G. Influent	Rinse Blank	Travel Blank	Trip Blank
Neutral Drugs							
Caffeine	1.250 (±0.039)	7.200 (±0.247)	1.563 (±0.0.79)	24.400 (±2.263)	0.011	0.026	0.002
Carbamazepine	0.666 (±0.055)	0.321 (±0.010)	0.024 (±0.002)	0.090 (±0.020)	N.D.	N.D.	N.D.
Cotinine	0.122 (±0.006)	2.028 (±0.117)	0.188 (±0.020)	0.292 (±0.008)	N.D.	N.D.	N.D.
Cyclophosphamide	0.006 (±0.0005)	0.018 (±0.0003)	N.D.	N.D.	N.D.	N.D.	N.D.
Fluoxetine	0.02 (±0.0002)	0.02 (±0.004)	N.D.	N.D.	N.D.	N.D.	N.D.
Pentoxifylline	0.031 (±0.0002)	0.007 (±0.0001)	N.D.	N.D.	N.D.	N.D.	N.D.
Trimethoprim	1.968 (±0.087)	12.000 (±0.141)	0.109 (±0.004)	0.012 (±0.0006)	N.D.	N.D.	N.D.
Acidic Drugs							
Bezafibrate	0.164 (±0.005)	0.407 (±0.017)	1.823 (±0.135)	NA	N.D.	N.D.	N.D.
Clofibric Acid	N.D.	N.D.	N.D.	NA	N.D.	N.D.	N.D.
Diclofenac	0.121 (±0.013)	0.285 (±0.049)	0.189 (±0.011)	NA	N.D.	N.D.	N.D.
Fenoprofen	N.D.	N.D.	N.D.	NA	N.D.	N.D.	N.D.
Gemfibrozil	0.086 (±0.0005)	0.169 (±0.035)	2.111 (±0.175)	NA	N.D.	N.D.	N.D.
Ibuprofen	0.279 (±0.006)	4.465 (±0.941)	2.889 (±0.116)	NA	N.D.	N.D.	N.D.
Indomethacin	0.30 (±0.002)	0.05 (±0.010)	0.85 (±0.151)	NA	N.D.	N.D.	N.D.
Ketoprofen	N.D.	N.D.	N.D.	NA	N.D.	N.D.	N.D.
Naproxen	0.963 (±0.053)	1.762 (±0.362)	2.219 (±0.000)	NA	N.D.	N.D.	N.D.
Sulfonamides							
Sulfacetamide	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Sulfapyridine	0.022 (±0.005)	0.206 (±0.012)	0.115 (±0.003)	N.D.	N.D.	N.D.	N.D.
Sulfadiazine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Sulfamethoxazole	3.050 (±0.278)	21.291 (±0.542)	0.677 (±0.012)	0.041 (±0.009)	N.D.	N.D.	N.D.
Sulfisoxazole	N.D.	N.D.	N.D.	0.023 (±0.010)	N.D.	N.D.	N.D.
Sulfamethazine	N.D.	N.D.	N.D.	0.018 (±0.0005)	N.D.	N.D.	N.D.
Fluoroquinolones							
Ciprofloxacin	0.107 (±0.011)	0.989 (±0.048)	1.408 (±0.009)	0.532 (±0.174)	N.D.	N.D.	N.D.
Norfloxacin	N.D.	0.467 (±0.035)	0.499 (±0.015)	0.216 (±0.010)	N.D.	N.D.	N.D.
Ofloxacin	0.466 (±0.031)	0.488 (±0.050)	0.223 (±0.006)	0.163 (±0.012)	N.D.	N.D.	N.D.

Appendix B.
Table 2. Relative standard deviations for PhAC analyses (%).

Compound	Kitchener Effluent	Kitchener Influent	Foxboro G. Effluent	Foxboro G. Influent
Neutral Drugs				
Caffeine	3.1	3.43	5.1	9.27
Carbamazepine	8.3	3	8	22
Cotinine	5	5.77	11	3
Cyclophosphamide	8	2	N.D.	N.D.
Fluoxetine	1	21	N.D.	N.D.
Pentoxifylline	0.6	1	N.D.	N.D.
Trimethoprim	4.4	1.18	4	5
Acidic Drugs				
Bezafibrate	3	4.2	7.41	N.A.
Clofibric Acid	N.D.	N.D.	N.D.	N.A.
Diclofenac	11	17	5.8	N.A.
Fenoprofen	N.D.	N.D.	N.D.	N.A.
Gemfibrozil	0.6	21	8.29	N.A.
Ibuprofen	2	21.1	3.88	N.A.
Indomethacin	0.7	22	17.8	N.A.
Ketoprofen	N.D.	N.D.	N.D.	N.A.
Naproxen	5.5	20.5	0.00	N.A.
Sulfonamides				
Sulfacetamide	N.D.	N.D.	N.D.	N.D.
Sulfapyridine	23	5.8	3	N.D.
Sulfadiazine	N.D.	N.D.	N.D.	N.D.
Sulfamethoxazole	9.11	2.55	1.8	22
Sulfisoxazole	N.D.	N.D.	N.D.	43
Sulfamethazine	N.D.	N.D.	N.D.	3
Fluoroquinolones				
Ciprofloxacin	11	4.9	0.6	32.7
Norfloxacin	N.D.	7.5	3.0	4.6
Ofloxacin	6.7	10	3	7.4

Appendix B
Table 3. Detection limits for pharmaceutical analytes in wastewater

	Instrument Detection Limit (ng/mL)	Method Detection Limit (ng/L)	Instrument Detection Limit (ng/mL)	Method Detection Limit (ng/L)
	Effluent		Influent	
Neutral Drugs				
Caffeine	1.4	3.5	1.2	6
Carbamazepine	0.07	0.175	0.05	0.125
Cotinine	0.4	1	0.6	1.5
Cyclophosphamide	1	2.5	0.5	1.25
Dihydroxycarbamazepine	0.6	1.5	0.6	1.5
Fluoxetine	5	12.5	2	5
Pentoxifylline	0.8	2	0.5	1.25
Trimethoprim	0.7	1.75	1	2.5
	Effluent		Influent	
Acidic Drugs				
Bezafibrate	0.9	2.25	0.8	2
Clofibric Acid	0.5	1.25	0.5	1.25
Diclofenac	2.8	7	2.9	7.25
Fenoprofen	6	15	3	7.5
Gemfibrozil	0.3	0.75	0.3	0.75
Ibuprofen	4	10	2	5
Indomethacin	15	37.5	10	25
Ketoprofen	3	7.5	3	7.5
Naproxen	3	7.5	2	5
	Effluent		Influent	
Sulfonamides				
Sulfacetamide	6	15	6	15
Sulfapyridine	2	5	2	5
Sulfadiazine	0.8	2	1.5	3.75
Sulfamethoxazole	0.5	1.25	0.8	2
Sulfisoxazole	0.5	1.25	0.5	1.25
Sulfamethazine	0.6	1.5	1	2.5
	Effluent		Influent	
Fluoroquinolones				
Ciprofloxacin	2.5	6.25	2.5	6.25
Norfloxacin	3.3	8.25	3.3	8.25
Ofloxacin	1	2.5	1	2.5

Appendix C: Questionnaire for social surveys in Kitchener and Foxboro

Questionnaire: Pharmaceuticals in the Environment

Please answer the questions by circling the answer where a choice is given, or by filling in the blank where there is a blank. Please circle only one answer unless the question asks you to do otherwise.

1. Often people have medications that are expired or that they do not intend to use, which they need to dispose of. How often do you dispose of unused or expired medication (both prescription and non-prescription drugs)?

a) daily

b) weekly

c) monthly

d) yearly

e) almost never – I almost never have unused or expired medications

2. If you dispose of unused or expired medications, which of the following methods do you use to dispose of them? Circle all the methods you use.

a) flushing down toilet or sink

b) throwing in garbage

c) return to the pharmacy

d) other _____

3. Before reading this questionnaire, were you aware that you could return your unused medications to the pharmacy for proper disposal?

a) yes

b) no

4. How much do you agree or disagree with the following statement: "Taking my unused or expired medication to the pharmacy for disposal would be inconvenient."?

a) strongly agree

b) agree somewhat

c) neither agree nor disagree

d) disagree somewhat

e) strongly disagree

5. Before reading this questionnaire, were you aware that pollution of rivers and streams by pharmaceuticals was an environmental concern?

a) yes

b) no

6. How much would you be willing to pay per year to improve sewage treatment so that river and stream pollution by pharmaceuticals could be reduced?

a) nothing

b) less than $10

c) $10-$24.99

d) $25-$49.99

e) $50 or more

7. Improving sewage treatment methods can reduce many types of river and stream pollution (including pollution by pharmaceuticals). Knowing that improved sewage treatment can generally improve the quality of stream and river water, how much would you be willing to pay per year to improve sewage treatment?

a) nothing

b) less than $10

c) $10-$24.99

d) $25-$49.99

e) $50 or more

8. How much do you agree or disagree with the following statement: "We should only spend money on environmental problems that affect human health, not on problems that only affect other species or ecosystems."

a) strongly agree

b) agree somewhat

c) neither agree nor disagree

d) disagree somewhat

e) strongly disagree

9. How much do you agree or disagree with the following statement: "We should try to prevent all water pollution, even if we have no evidence that a pollutant will harm human or ecosystem health."

a) strongly agree

b) agree somewhat

c) neither agree nor disagree

d) disagree somewhat

e) strongly disagree

10. How much do you agree or disagree with the following statement: "If an environmental problem doesn't affect my health or my property, I don't care about it."

a) strongly agree

b) agree somewhat

c) neither agree nor disagree

d) disagree somewhat

e) strongly disagree

11. If one of the medications you take were bad for the environment, would you be willing to switch to a more environmentally friendly medication?

a) definitely

b) probably

c) not sure

d) probably not

e) definitely not

12. How would you rank the following 5 items in terms of how important they are to you? Rank the items from 1 to 5, with 1 being the most important and 5 the least important.

_____ Human Health

_____ Education

_____ The Environment

_____ Jobs

_____ Transportation (Roads, public transit, etc.)

13. To understand which pharmaceuticals could enter the environment, it is important for us to know which types of pharmaceuticals (medications) you take frequently. Which prescription drugs have you taken over the past year, and how often do you take them? Please circle the ones you have taken and write in how often you have taken them.

drug	_how often?_
a) cholesterol medication	_____
b) pain medication	_____
c) chemotherapy	_____
d) heart medication	_____
e) antibiotics	_____
f) hormones	_____
g) other	_____

14. Which non-prescription drugs (ex: aspirin, ibuprofen) do you take, and how often do you take them? Please circle the ones you have taken over the past year, and write in how often you have taken them.

drug	_how often?_
a) ASA (Aspirin)	_____
b) Acetominophen (Tylenol)	_____

c) Ibuprofen   _____

d) Herbal medications   _____

e) Cough & cold medications   _____

f) Anti-histamines   _____

g) Other   _____

15.   In order to compare your responses with those of people from both similar and different backgrounds, we need to ask a few standard questions. Could you tell us how old you are?

a) 18-30

b) 31-45

c) 46-60

d) over 60

16. Are you male or female? M F

17. What is the highest level of education you have completed?

     a) public/elementary school

     b) some high school

     c) graduated high school

     d) some vocational/college

     e) graduated vocational/college

     f) some university

     g) graduated university

     h) post-graduate degree

Thank you for your assistance with this study!

Appendix D: Photos from Kitchener and Foxboro WWTPs

1. Solids removal, Kitchener

.

2. Deflocculation, Kitchener WWTP

3. Aeration, Kitchener WWTP

4. Clarification, Kitchener WWTP

5. Chlorination, Kitchener WWTP

6. Settling Ponds, Kitchener WWTP
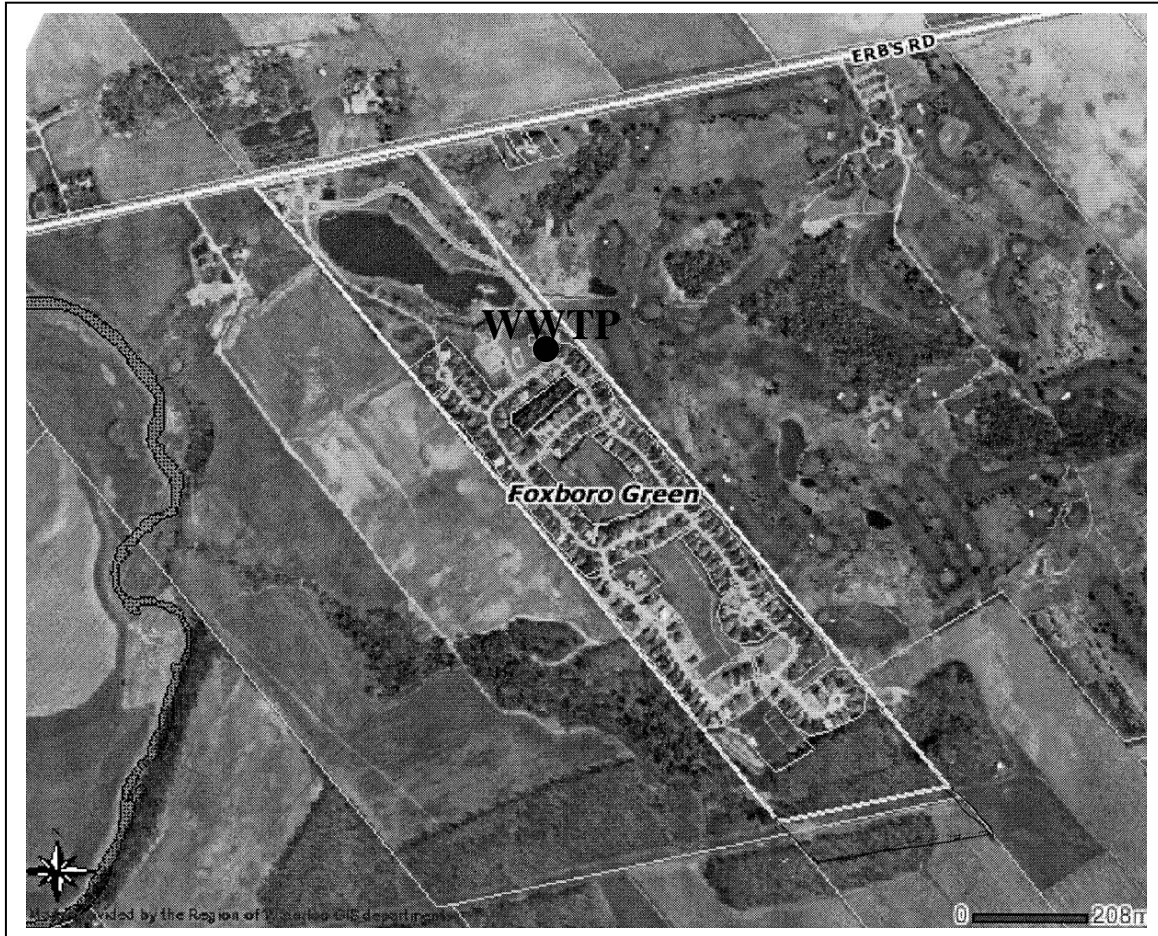

7. Influent sampling, Kitchener WWTP

7. Foxboro WWTP

8. Foxboro WWTP

9. Aerial view of Foxboro, showing WWTP

Appendix E: Interviews – Scientific/Management Experts

1) By whom are you employed?
a) a university
b) government
c) private company/industry
d) NGO
e) other _____

2. What is your field of specialty (ex: toxicology, hydrogeology)?

3. Where do you live?
a) Canada
b) the United States
c) Europe
d) other_____

4. Do you see the contamination of surface water and groundwater by pharmaceuticals as:
a) a human health concern only
b) a concern for aquatic ecosystems only
c) both a human health concern and a concern for aquatic ecosystems
d) neither a human health concern nor a concern for aquatic ecosystems
e) other _____

Would you like to elaborate?

5. How important or unimportant do you think it is for your country's government to take action to reduce the release of pharmaceuticals to the environment?
a) very important
b) somewhat important
c) neither important nor unimportant
d) somewhat unimportant
e) very unimportant

Why? Please elaborate.

6. a) Is your country's government currently taking action to reduce the release of pharmaceuticals to the environment? If so, what is the action, and how do you feel about it?

b) Is your government conducting research on pharmaceuticals in the environment? If so, what type of research?

7. a) Do you support the use of the Precautionary Principle in environmental decision-making? (Precautionary Principle as defined in the Rio Declaration: 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)? Why or why not?

b) What, in your view, does the Precautionary Principle mean for pharmaceuticals in the environment?

8. Which policies or management techniques would you like to see used to reduce environmental contamination by pharmaceuticals?

9. How, in your opinion, does surface and groundwater contamination by pharmaceuticals compare to other concerns regarding water quality?

10. Please rank the following surface and groundwater contaminants in order of greatest concern/need for action in your country. Rank the issue that you believe needs the most attention/action as 1, and the issue that you believe needs the least attention/action as 7.

___ road salt
___ pharmaceuticals
___ metals
___ pathogens
___ pesticides
___ organic solvents
___ nutrients (nitrate, phosphate)

Would you like to add comments to your ranking?

11. What do you see as the priority research areas regarding pharmaceuticals in the environment?

12. On a scale of 1 to 5, how much scientific uncertainty is associated with the effects of pharmaceuticals on aquatic ecosystems, with 1 representing no uncertainty, and 5 representing complete uncertainty? ___

Why?

13. How likely do you think it is that pharmaceuticals in surface water and groundwater will cause serious or irreversible damage to aquatic ecosystems?
a) very likely
b) somewhat likely
c) neither likely nor unlikely
d) somewhat unlikely
e) very unlikely

14. How likely do you think it is that pharmaceuticals in surface water and groundwater will cause serious or irreversible damage to human health?
a) very likely
b) somewhat likely
c) neither likely nor unlikely
d) somewhat unlikely
e) very unlikely

15. What is your view of the following management strategies?

a) Require all wastewater treatment plants in your country to use secondary treatment as a minimum

b) Environmental risk assessments for pharmaceuticals, for registration purposes

c) Enhanced treatment methods (membrane filtration, ozonation, AOP, etc.) for municipal sewage

d) Ban use of antibiotics and hormones as agricultural growth promoters

e) Incentives for pharmaceutical research companies to develop 'green' drugs

f) Keep hospital wastewater separate and treat with advanced methods (ozonation, membrane filtration)

g) Best management practices in agriculture: Improved controls on spreading of manure, location of livestock

h) Pharmaceutical returns programs: Organization of returns programs and education to encourage people to return their drugs

i) Upgrade to advanced sewage treatment in high-use areas such as retirement communities

j) Education of physicians and veterinarians to reduce over-prescription of pharmaceuticals

k) Optimization of existing wastewater treatment plants to better remove pharmaceuticals (without upgrading technology)

l) Other?

16. For these same management techniques, please assign a score on a scale of 1 to 10 in terms of effectiveness at preventing environmental impacts from pharmaceuticals, and in terms of feasibility of implementation:

a) Require all wastewater treatment plants in your country to use secondary treatment as a minimum

effectiveness:
feasibility:

b) Environmental risk assessments for pharmaceuticals, for registration purposes

effectiveness:
feasibility:

c) Advanced treatment methods (membrane filtration, ozonation, etc.) for municipal sewage

effectiveness:
feasibility:

d) Ban use of antibiotics and hormones as agricultural growth promoters

effectiveness:
feasibility:

e) Incentives for pharmaceutical research companies to develop 'green' drugs

effectiveness:
feasibility:

f) Keep hospital wastewater separate and treat with advanced methods (ozonation, membrane filtration)

effectiveness:
feasibility:

g) Best management practices in agriculture: Improved controls on spreading of manure, location of livestock

effectiveness:
feasibility:

h) Pharmaceutical returns programs: Organizatin of returns programs and education to encourage people to return their drugs

effectiveness:
feasibility:

i) Upgrade to tertiary treatment in high-use areas such as retirement communities

effectiveness:
feasibility:

j) Education of physicians and veterinarians to reduce over-prescription of pharmaceuticals

effectiveness:
feasibility:

k) Optimization of existing wastewater treatment plants to better remove pharmaceuticals (without upgrading technology)

effectiveness:
feasibility:

l) Other?

effectiveness:
feasibility:

17. Do you have any further comments you would like to make on the topic of pharmaceuticals in the environment?

Appendix F: Interviews – Pharmaceutical Industry

1. Where do you live?
a) Canada
b) the United States
c) the European Union
d) other _____

2. Do you see the contamination of surface water and groundwater by pharmaceuticals as:
a) a human health concern only
b) a concern for aquatic ecosystems only
c) both a human health concern and a concern for aquatic ecosystems
d) neither a human health concern nor a concern for aquatic ecosystems
e) other _____

Would you like to elaborate?

3. How important or unimportant do you think it is for your government to take action to reduce the release of pharmaceuticals to the environment?
a) very important
b) somewhat important
c) neither important nor unimportant
d) somewhat unimportant
e) very unimportant

Why? Please elaborate.

4. a) Is your country's government currently taking action to reduce the release of pharmaceuticals to the environment? If so, what is the action, and how do you feel about it?

5. What, in your view, does the Precautionary Principle mean for pharmaceuticals in the environment? (Precautionary Principle as defined in the Rio Declaration: 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)

6. How likely do you think it is that pharmaceuticals in surface water and groundwater will cause serious or irreversible damage to aquatic ecosystems?
a) very likely
b) somewhat likely
c) neither likely nor unlikely
d) somewhat unlikely
e) very unlikely

7. How likely do you think it is that pharmaceuticals in surface water and groundwater will cause serious or irreversible damage to human health?
a) very likely
b) somewhat likely
c) neither likely nor unlikely
d) somewhat unlikely
e) very unlikely

8. Several countries have developed, or are in the process of developing, environmental assessment regulations for human and veterinary pharmaceuticals.
a) As a representative of the pharmaceutical industry, do you feel it is a good idea to have such regulations, and why/why not?

b) Do you have any specific concerns with regard to these regulations?

c) What do you believe the end products of environmental assessments for pharmaceuticals should be? For example, should the purpose simply be to generate information for a database? Or should management action such as labelling or removing a substance from the market be a possible outcome?

9. Several other ways of managing pharmaceuticals in the environment have been suggested by researchers. One of these is to have pharmaceutical returns programs, whereby customers would return their unused medications to the pharmacy or another location for disposal.
 a) In your opinion, would your organization likely be willing to contribute to the development of a drug returns program, or to an education program, to encourage people to return their unused drugs to the pharmacy (or another location)? Why/why not?

b) Pharmaceuticals are also used in agriculture. Would your organization likely be willing to contribute to a program by which farmers could return their unused medication to a central location, for disposal by incineration?

10. Another way of minimizing environmental contamination by pharmaceuticals would be to improve sewage treatment. Research conducted as part of my study suggests that some members of the public feel the pharmaceutical industry should contribute to any upgrading of sewage treatment plants to improve the removal of pharmaceuticals. Do you think your organization would be willing to contribute financially to the upgrading of sewage treatment plants, to prevent pharmaceuticals from entering streams and rivers? Why/why not?

11. Some people have suggested that the pharmaceutical industry should try to manufacture more 'green' drugs. These environmentally friendly drugs would be more biodegradable and less harmful to aquatic organisms like fish. How feasible do you think it would be to develop 'green' drugs…
a) from a scientific perspective?

b) from a financial/R&D funding perspective?

c) How likely do you think the pharmaceutical industry is to try to develop 'green' drugs, of its own volition/due to public and market pressure, and why?

d) Given incentives from government, how likely do you think the pharmaceutical industry is to try to develop 'green' drugs, and why?

e) What sort of incentives would the pharmaceutical industry require to increase its efforts to develop 'green' drugs?

12. As a representative of a pharmaceutical company, what is your opinion on the following potential management strategies to reduce the release of pharmaceuticals to the environment? Please give each management strategy a score out of 10 based on (in your opinion) how much the pharmaceutical industry would like to see the management strategy implemented, with 10 meaning the pharmaceutical industry would definitely support its implementation, and 1 meaning the pharmaceutical industry would definitely not support its implementation. Please also give your opinion of the management strategy verbally.

a) Require all wastewater treatment plants in your country to use secondary treatment as a minimum.
Opinion:

Score out of 10:

b) Environmental risk assessments for pharmaceuticals, for registration purposes

Opinion:

Score out of 10:

c) Enhanced treatment methods (membrane filtration, ozonation, AOP, etc.) for municipal sewage
Opinion:

Score out of 10:

d) Ban use of antibiotics and hormones as agricultural growth promoters
Opinion:

Score out of 10:

e) Incentives for pharmaceutical research companies to develop 'green' drugs
Opinion:

Score out of 10:

f) Keep hospital wastewater separate and treat with advanced methods (ozonation, membrane filtration)
Opinion:

Score out of 10:

g) Best management practices in agriculture: Improved voluntary controls on spreading of manure, location of livestock, use of pharmaceuticals
Opinion:

Score out of 10:

h) Pharmaceutical returns programs: Develop returns programs & educate people to return their drugs to the pharmacy (or other location).
Opinion:

Score out of 10:

i) Upgrade to tertiary treatment in high-use areas such as retirement communities

Opinion:

Score out of 10:

j) Education of physicians and veterinarians to reduce over-prescription of pharmaceuticals
Opinion:

Score out of 10:

k) Optimization of existing wastewater treatment plants to better remove pharmaceuticals
Opinion:

Score out of 10:

l) Other? _____
Opinion

Score out of 10:

13. Do you have any other comments you would like to add on the topic of pharmaceuticals in the environment?