Science of the Total Environment 646 (2019) 257–264

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Environmental loadings of Active Pharmaceutical Ingredients from manufacturing facilities in Canada

Sonya Kleywegt [a,*], Mark Payne [b], Fai Ng [b], Tim Fletcher [a]

[a] Ontario Ministry of the Environment and Climate Change, ON, Canada
[b] Environmental Services, The Regional Municipality of York, Newmarket, ON, Canada

HIGHLIGHTS

- Direct discharges from pharmaceutical facilities are a key source of pollution to receiving sewersheds.
- Elevated concentrations of pharmaceuticals are detected in effluents from manufacturers.
- Facilities may be discharging several kilograms of lost product directly to the sewers daily.

ARTICLE INFO

Article history:
Received 2 May 2018
Received in revised form 11 July 2018
Accepted 17 July 2018
Available online xxxx

Editor: Ching-Hua Huang

Keywords:
Pharmaceutical manufacturers
Active Pharmaceutical Ingredients (APIs)
Sewershed
Sewage treatment plant (STP)

ABSTRACT

Recent evidence has revealed that cities with pharmaceutical manufacturers have elevated concentrations of Active Pharmaceutical Ingredients (APIs) in their receiving water bodies. The purpose of this study was to gather information on direct sewer discharges of APIs during their manufacturing and processing from five pharmaceutical manufacturing facilities in Ontario, Canada. Drug classes and maximum reported concentrations (ng/L) for which APIs were directly discharged included: antidepressants (paroxetine - 3380 and sertraline - 5100); mood stabilizer (carbamazepine - 575,000); antibiotics (penicillin - 14,300); analgesics (acetaminophen - 461,000; codeine - 49,200; ibuprofen - 344,000; naproxen - 253,000 and oxycodone 21,000); cardiovascular drugs (atorvastatin - 893 and metoprolol - 7,333,600) and those drugs used for blood pressure control (amlodipine - 22,900; diltiazem - 1,160,000; furosemide - 1,200,000 and verapamil - 7340). Based on flow and water usage data from the individual facilities, the maximum concentrations for acetaminophen, ibuprofen, carbamazepine, diltiazem and metoprolol correlate to approximately 200, 220, 390, 420 and 14,200 g respectively, of lost product being directly discharged to the sewers daily during active manufacturing. This survey demonstrates that direct point source discharges from pharmaceutical manufacturers represent a key source of pharmaceutical pollution to receiving sewersheds. Onsite recovery of product or treatment at pharmaceutical manufacturing or processing facilities to reduce the sewage loadings to receiving treatment plants, product loss and potential environmental loadings is strongly recommended.

1. Introduction

It is generally recognized that water bodies act as sinks for various forms of pollution including administered human pharmaceuticals that are excreted to the environment either as parent compounds or metabolic by-products via wastewater (Daughton and Ternes, 1999; Kümmerer, 2009 and Williams et al., 2016). Sewage treatment plant (STP) effluent is widely regarded as the primary pathway for human pharmaceutical compounds to enter the aquatic environment (Daughton and Ternes, 1999 and Donnachie et al., 2016). Although a number of studies assessing the presence and occurrence of these compounds in municipal sewage have been published, including those in Canada (Metcalfe et al., 2003, 2010, and Lishman et al., 2006), the focus has been on the occurrence and efficacy of reduction due to treatment processes that occur at these plants, rather than the types of sources that may be the leading contributors of APIs to the STPs. It is well known and accepted that STPs were not designed for the reduction and/or removal of such compounds. Conventional activated sludge processes were designed for the removal of carbon, nitrogen and phosphorous (compounds with high biological degradation, hydrophobic properties and low polarity). In contrast, APIs often have specific biological activity at low concentrations (ng/L), are stable and hydrophilic.

* Corresponding author at: Technical Assessment and Standards Development Branch, Ontario Ministry of the Environment and Climate Change, 40 St. Clair Ave. West, 7th floor, Toronto, ON M4V 1M2, Canada.
E-mail address: sonya.kleywegt@ontario.ca (S. Kleywegt).

https://doi.org/10.1016/j.scitotenv.2018.07.240
0048-9697/

In fact, little information is available regarding the contribution of APIs and other emerging contaminants (ECs) to sewersheds from the industrial, commercial and institutional (ICI) sectors (Lin et al., 2008; Sim et al., 2011; Cardoso et al., 2014; Aus Der Beek et al., 2015; Larsson, 2015 and Kleywegt et al., 2015).

In general, the wastewater discharge of contaminants from ICI facilities to the sewer system in the province of Ontario, Canada is regulated at the municipal (city) level of government. Each municipality is able to set their own sewer-use bylaw limits for ICI facilities that discharge directly to the receiving STP. Sewer-use bylaws may be different for each city in the Province of Ontario and generally have concentration limits for conventional parameters like metals, nutrients, some organics and pH. Typically these limits apply to all businesses in the municipality and are not specific to different types of industrial or commercial facilities. In addition, most receiving STPs are owned and operated at the municipal level of government as well.

Both the Provincial and Federal governments regulate the discharges from STPs to receiving bodies, the federal government through the Water Systems Effluent Regulation (WSER), and Ontario through the use of regulated effluent limits in Environmental Compliance Approvals (ECAs). However, effluent discharge limits for STPs are generally limited to conventional parameters like metals, nutrients, oxygen demand and some organics. Recent studies in Canada have demonstrated that higher levels of sewage treatment (nitrification/denitrification and increased retention time) can have significant impacts on the reduction of known concentrations of APIs in the final effluent with a subsequent decrease in downstream environmental impacts, such as intersex of fish (Brown et al., 2011; Parker et al., 2014 and Hicks et al., 2017).

To date, discharges of APIs during the manufacturing and processing of pharmaceutical products and their total source contribution to a receiving sewershed has been under-investigated as a direct point source to the environment, with only limited studies currently available worldwide (Qiting and Xiheng, 1988; Bisarya and Patil, 1993; Holm et al., 1995; Reddersen et al., 2002; Zuhlke et al., 2004; Lin et al., 2008; Bernard and Arnold, 2009; Ortelli et al., 2009; Phillips et al., 2010; Sim et al., 2011 and Gasser et al., 2012). In fact, effluents from pharmaceutical factories can contain high concentrations of API's (Lin et al., 2008; Carlson et al., 2009 and Cardoso et al., 2014) and can often exceed aquatic toxicity thresholds (concentrations) (Carlson et al., 2009 and Sanchez et al., 2011). Because production is concentrated in specific locations, the risks cannot be linked to usage patterns. Furthermore, since the pharmaceuticals are not being consumed, metabolism in the human body does not reduce concentrations. For these reasons, any risk management measures and/or actions to reduce or eliminate the release of APIs from active manufacturing or processing (production) versus from human excretion (sewage treatment) differ in terms of accountability, incentive, creation, legal opportunities and costs (Larsson, 2015).

The first series of papers documenting elevated concentrations of pharmaceuticals from drug manufactures were from China and India, which provide half of the world production of API's (Qiting and Xiheng, 1988 and Bisarya and Patil, 1993). Further evidence was presented from studies conducted in Taiwan and Korea (Lin et al., 2008; Sim et al., 2011), the United States (Phillips et al., 2010), Switzerland (Bernard and Arnold, 2009 and Ortelli et al., 2009); Israel (Jerusalem) (Gasser et al., 2012); Germany (Zuhlke et al., 2004) and Denmark (Holm et al., 1995), where select API concentrations were reported in the mg/L range.

To date, only one study has been conducted in North America (New York State). This study evaluated the contribution of an API manufacturer to a receiving STP over several years (Phillips et al., 2010). It was shown that the manufacturer represented approximately 20% of the flow to the receiving STP and that elevated concentrations of select opioids were 30–500 times higher than those concentrations found at other STPs (without active manufacturing or processing of APIs).

Given the expense of treating all municipally-derived wastewaters to reduce and/or remove APIs for which they were not designed, understanding the sources of pharmaceuticals to the receiving STP is important for the development of potential future risk management approaches. For instance, it may be more cost effective to require pretreatment at significant point sources (healthcare or manufacturing facilities), if they can be identified, than at the STP as has been previously suggested (Pauwels et al., 2008 and Caldwell et al., 2016).

In building upon the unknown extent of the loading from pharmaceutical manufacturing facilities in North America, the primary objective of the present study was to determine the concentrations of select APIs directly discharged to sewers from pharmaceutical manufacturers during active manufacturing and processing of known APIs in Canada and to provide pharmaceutical manufacturers, STP operators, regulators and designers with data regarding possible API loadings from manufacturers. Our results provide further evidence that direct effluents from pharmaceutical facilities represent a key source and loading of APIs to receiving sewersheds and may be a significant source loading to a receiving STP. It is recommended that pharmaceutical manufacturers and regulators at all levels consider monitoring the direct effluent from these facilities and consider on-site treatment to reduce STP loading, and environmental risk.

2. Methods and materials

2.1. Pharmaceutical manufacturing and processing facilities

A total of five individual facilities were monitored in this study (Table 1). None of the participating facilities had on-site treatment for APIs prior to discharging to the sewershed. Samples were collected at the first sewer maintenance access hole leaving each facility. Samples analyzed from each of the facilities are eventually treated downstream at a municipal STP, prior to discharging to a receiving environment (Lake Ontario).

The types of APIs that were being manufactured and, or processed at the facilities at the time of sampling are provided in Table 2. Some facilities (1 and 5) had two separate effluent streams to the receiving sewershed and thus both were sampled but on different days. Grab samples were also collected from the internal manufacturing process lines at some facilities (1, 2 and 3) in order to establish the level of manufactured APIs entering the facility waste stream or final effluent discharged to the sewers (Table 2 and S2).

2.2. Sample collection

All sewer maintenance access hole samples were collected between June and November of 2016 using portable automatic field composite samplers (automatic samplers) following the municipality's normal wastewater sampling protocols. New internal (silicone) and external tubing (clear polyvinyl chloride, Klearon Series K010, Kuri-Tech) were used for the automatic samplers. Automatic samplers were set up at

Table 1
Characteristics of facilities sampled (1–5) including the number of employees; water usage at the facility including annual water consumption (m3); estimated daily flow rates (QL/d) and mean daily flow rate (L/s and L/d).

Facility	Number of employees	Annual water consumption for 2016 (m3)	Estimated daily mean wastewater generated as a daily flow rate (Q L/d)	Measured mean daily flow rate (L/s)	Mean daily flow rate (L/d)
1 A	600	43,935	68,340	2.2	190,000
1 B				2.7	216,000
2	200	70,197	192,321	2.4	207,360
3	200	163,992	449,293	5.2	449,280
4	1380	234,742	643,128	NA	
5A	1500	132,915	364,150	NA	
5B		132,915	364,150	NA	

NA – not applicable. Flow meters could not be utilized at these sampling locations.