Human Health Risk Assessment of Exposure to Emerging Contaminants (Pharmaceuticals and Personal Care Products) in Drinking Water Supply in Non-Sewered Communities

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ABSTRACT

Pharmaceuticals and personal care products (PPCPs) are continuously released into the environment following regular household use. With the improvement in analytical techniques, research addressing the occurrence, fate and effects of these compounds in various environmental media has increased over the last two decades. There is however, a significant knowledge gap regarding environmental exposure to PPCPs for different regions particularly low-to-middle income countries and emissions from sources other than wastewater treatment plants (WWTPs), such as Onsite wastewater treatment systems (OWTSs).

A cross-sectional survey of 350 households in southern Nigeria was used as a proxy to estimate the annual household use of personal care products (PCPs) and the mass of active pharmaceutical ingredients (APIs) consumed per capita per year by applying the WHO Defined Daily Dose concept. Paracetamol was the most widely consumed API with average per capita use of 92.7 g/year.

A risk-based prioritization scheme was developed to pre-select PPCPs with the greatest potential to enter groundwater from septic systems using the risk index (RI) approach. The developed priority list of PPCPs indicates that 14 APIs and 9 PCP active ingredients have RI ≥ 0.01 and are therefore considered high priority compounds for future groundwater monitoring protocols in southern Nigeria.

A comprehensive monitoring protocol was developed to characterize the occurrence and concentrations of dichlorvos (a household pesticide) and 61 APIs in domestic water wells impacted by septic systems in southern Nigeria. All sampled wells (53) had detected levels of at least 2 APIs and the six most frequently detected (>50%) APIs included paracetamol, sulfamethoxazole, trimethoprim, carbamazepine, naproxen and caffeine, with maximum concentrations (MEC_{max}) estimated at 982 ng/L, 1253 ng/L, 193 ng/L, 445 ng/L, 234 ng/L and 962 ng/L respectively. Dichlorvos was detected in 12 out of 20 sampled wells at concentrations ranging from 1.88 ng/L to 68.4 ng/L.

Finally, the risk of potential adverse effects from indirect exposure to APIs in drinking water was assessed by benchmarking exposure with the derived acceptable daily exposure (ADE) limits for individual APIs. Hazard quotient (HQ) was less than 1 for all APIs, which suggests that exposure to maximum levels of individual APIs in Nigerian groundwater currently do not pose an appreciable risk to human health. However, long term exposure to trace levels of chemical mixtures in drinking water may result in a relatively greater risk than that posed by individual substances due to potential for cocktail effects and underscores the need for further investigation.

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To God be the Glory.

Author Declaration

The work in this thesis was undertaken as a PhD student in the Department of Environment and Geography, University of York. The Research was funded by the Tertiary Education Trust Fund (TETFUND) Nigeria. I declare that this thesis is a presentation of my original work and that the contents have been produced solely by the candidate. This work has not previously been presented for an award at this or any other university. All sources are acknowledged as references.

The data reported in Chapters 3 and 4 were presented at the SETAC Europe 28th annual meeting, Rome, Italy, 2018.

Chapters 2 to 6 have been written as papers for international peer-reviewed journals. The current publication status of the papers is presented in Table 0.1. All these papers have been reworked so they can be presented in a consistent style and format in this thesis.

Table 0. 1 Status of the papers presented in this thesis with respect to the publication process.

Chapter	Title	Journal	Status
2	Occurrence and fate of pharmaceuticals and personal care products in septic systems and impacted downgradient groundwater - A review	Critical Reviews in Environmental Science and Technology	In Preparation
3	Survey of household use and disposal practices of pharmaceuticals and personal care products in southern Nigeria	Toxics	In Preparation
4	Risk-based prioritization of pharmaceuticals and personal care products in groundwater in non-sewered communities	Environmental Toxicology and Chemistry	In Preparation
5 & 6	Monitoring of pharmaceuticals and home use pesticide (dichlorvos) in groundwater of southern Nigeria and assessment of human health risk]	Environmental Health Perspectives	In Preparation

Glossary

ACT	artemisinin combination therapy
ADE	acceptable daily exposure
ADI	acceptable daily intake
API	active pharmaceutical ingredients
ATC	anatomical therapeutic chemical
CVM	contingent valuation method
DOT	days of therapy
EPA	environmental protection agency
EOC	emerging organic contaminant
FDA	food and drug administration
GC/MS	gas chromatography–mass spectrometry
HPLC-MS/MS	high performance liquid chromatography tandem mass spectrometry
IDL	instrument detection limit
LC-MS	liquid chromatography mass spectrometry
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEL	lowest observed effect level
LOQ	limit of quantitation
MEC	measured environmental concentrations
MSD	mass selective detector
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OTC	over the counter
OWC	organic wastewater contaminant
OWTS	onsite wastewater treatment system
PBT	persistent, bio accumulative and toxic
PCP	personal care product
POD	point of departure
PEC	predicted environmental concentration
PPCP	pharmaceuticals and personal care product
QSAR	quantitative structure activity relationship
SPE	solid phase extraction

STE	septic tank effluent
SIM	selected ion monitoring
TDL	therapeutic dose level
WHO	world health organization
WTP	willingness to pay
WWTP	wastewater treatment plant

Chapter 1

Introduction

1.1 Pharmaceuticals and Personal Care Products in the Environment

In recent times, the focus of environmental research has extended beyond conventional priority pollutants such as persistent organic pollutants (POPs) to include the so-called emerging contaminants (ECs) which come from diverse products including pharmaceuticals, personal care products (PCPs), nanomaterials, pesticides, industrial compounds, fragrances and a range of other home use chemicals (Boxall, 2012; Jurado et al., 2012). ECs are not necessarily new substances but are a diverse group of bioactive chemicals currently without water quality regulations (Farré et al., 2008), have not been extensively monitored in the environment and have the capability to elicit known or potential adverse human health and / or ecological impacts (Boxall, 2012).

Trends in EC research include an increasing number of occurrence, fate, effects and risk studies of ingredients in pharmaceuticals and personal care products (often referred to as PPCPs) used in our everyday life (Boxall et al., 2012). This has resulted in an exponential increase in the number of publications documenting the widespread presence and distribution of a wide variety of PPCPs in various environmental media (Daughton, 2016), particularly in water bodies, including groundwater, surface water, wastewater and tap/drinking water (Kolpin et al., 2002; Stackelberg et al., 2004; Schwab et al., 2005; Conn et al., 2010; Benner et al., 2013; Cahill et al., 2016; Schaider et al., 2016).

Pharmaceuticals include numerous prescription and over-the-counter medicines and diagnostic agents which are in widespread use for disease diagnosis, prevention and treatment in humans (Daughton and Ternes, 1999). Personal care products (PCPs) include a wide range of products

used daily to promote the quality of life and include cosmetics (e.g. skin moisturizers, deodorants, shampoos, hair colors), fragrances (e.g. synthetic musk, perfumes), cleaning agents (e.g. disinfectants, surfactants), oral hygiene products (e.g. toothpaste, mouth wash), sun screen agents and insect repellents (e.g. DEET) (Boxall et al., 2012; Richardson et al., 2005; Ternes et al., 2004). The growing interest in PPCPs is prompted by their ubiquitous presence in the environment, their bioactive characteristics and the potential to occur as mixtures (Monosson, 2005), capable of exhibiting synergistic or additive effects even at trace levels (i.e. nanogram per litre (ng/L)) (Escher et al., 2002). In the following sections, an overview is given of the current knowledge on environmental exposure pathways and the human health effects of PPCPs, as well as the challenges and implications of current wastewater treatment technology in developing countries.

1.2 Sources and Pathways of PPCPs in the Environment

Several sources of PPCP input to the environment have been identified and important exposure routes include human wastes (Kolpin et al., 2002; Christensen, 1998), pharmaceutical wastes such as expired or unused medications (Bound and Voulvoulis, 2005), animal feeding operations (Boxall et al., 2012), agricultural and urban runoff (Pedersen and Yeager, 2003) and landfill leachates (Barnes et al., 2004). Active pharmaceutical ingredients (APIs) can enter the environment following patient use and subsequent excretion of intact or metabolized pharmaceuticals in urine or faeces and the disposal of unused medications through the toilet or sink (Daughton and Ruhoy, 2008). A wide range of down-the-drain PCPs used regularly for bathing, showering and household cleaning also end up in the environment in partially treated wastewater discharges (Ternes et al., 2004; Richardson et al., 2005).

Among the various sources of PPCPs in the environment (Figure 1.1), emissions from wastewater treatment systems are considered relatively more significant than those from landfills and agriculture (Daughton, 2003; Boxall, 2012; aus der Beek et al., 2016). The relative dominance

of urban wastewater emissions regarding environmental exposure to PPCPs may be attributed to the inherently limited treatment efficiency of conventional wastewater treatment systems, including municipal wastewater treatment plants (WWTPs) and decentralized onsite wastewater treatment systems (OWTSs), which are not typically designed to remove organic wastewater contaminants (OWCs) (Hinkle et al., 2005).

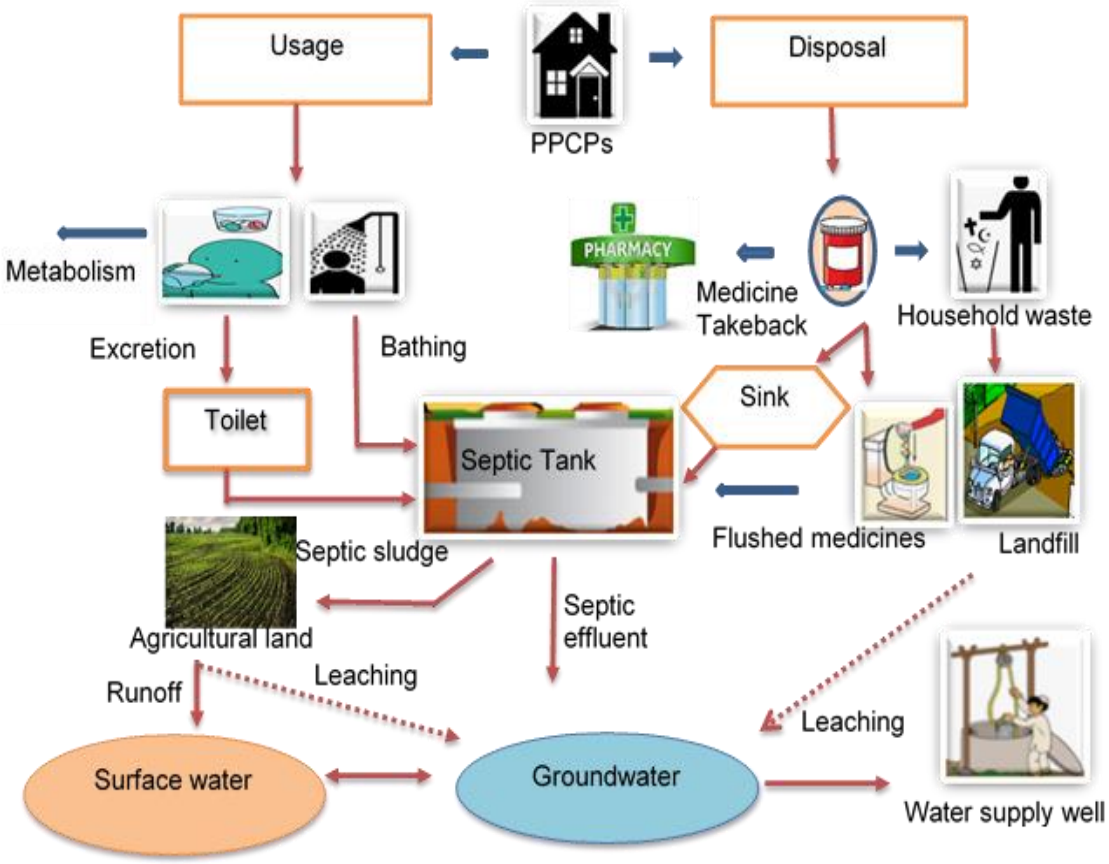


Figure 1. 1 Sources and pathways for groundwater pollution by PPCPs

Because wastewater treatment systems discharge large volumes of partially treated wastewater into the environment, there is continuous release of a variety of PPCPs to the environment

(Daughton, 2003); an important consequence of continuous environmental release of treated wastewater is that many PPCPs can migrate to locations far away from the source (Walters et al., 2010), and although some of these substances are inherently biodegradable, with minimal chemical stability, they can become 'pseudo-persistent' in the environment because they are replenished faster than they are removed (Daughton and Ternes, 1999; Daughton, 2002; Daughton, 2003). Wastewater treatment technologies therefore, constitute a dominant distribution and exposure pathway to the environment for a variety of PPCPs (Ternes et al., 2004; Godfrey & Woessner, 2004; aus der Beek et al., 2016).

1.3 Wastewater Treatment Technology in Nigeria, Challenges and Implications for Human Health

In many developed countries, domestic wastewater treatment is largely centralized, with the bulk of wastewater collected and treated in municipal WWTPs prior to discharge into receiving surface waters (Du et al., 2014). By contrast, in many developing countries, wastewater is treated predominantly by a decentralized approach, involving the use of onsite systems, also known as septic systems (Kookana et al., 2014). The demand for septic systems is rapidly growing in developing countries as a progression towards achieving the improved sanitation target of the United Nations Millennium Development Goals (MDGs) (Kjellen et al., 2011).

In Nigeria, the conventional septic tank system (STS) is the predominant onsite system used by approximately three in four households for treating wastewater (Adesogan, 2013). These traditional systems discharge partially treated effluent into the immediate surroundings and although it has been argued that septic systems provide a simple, cost effective and convenient alternative to municipal WWTPs, particularly in rural and suburban areas lacking access to centralized sewage collection and treatment facilities (Borchardt et al., 2003; Carrara et al., 2008; Lusk et al., 2011; Bremer & Harter, 2012; Ortiz De García et al., 2013; Kookana et al., 2014),

most septic systems, unlike municipal WWTPs, operate without performance monitoring and do not have discharge limits (Bradley et al., 2002). Other drawbacks relate to design, treatment and operating standards, which are not always available to many septic system users in developing countries. In Nigeria, for example, septic system use is not regulated by the government or any appointed agency, and consequently, Code of Practice and standards for proper design, construction, operation and maintenance of septic systems are unavailable to users. The status quo in Nigeria regarding septic system use and management raises concern about environmental and public health risks associated with the use of these systems, particularly the risk of contamination of groundwater used as a potable water source.

For example, in the United States, the Environmental Protection Agency (EPA) issues guidelines on septic system use and recommends adherence to the septic system Code of Practice to improve treatment performance and to minimize septic system failure (USEPA, 2002b). Likewise in Australia, local authorities assess and manage septic systems following stipulated septic system management standards (Carroll et al., 2006). A lack of a strong regulatory framework and standardized management strategies for onsite wastewater treatment may lead to poorly designed and improperly maintained septic systems, which may not sufficiently remove pollutants (particularly unconventional pollutants such as PPCPs), leading to the subsequent release of poorly treated or untreated wastewater to the environment (Siegrist et al., 2001; Cliver, 2000; Bremer & Harter, 2012; Hinkle et al., 2005; Conn et al., 2006; Godfrey et al., 2007; Stanford & Weinberg, 2010). Failing systems often lack optimal conditions necessary for effluent treatment, including physical filtration, adsorption, sedimentation, and contaminant attenuation in soil (Charles et al., 2005). In the United States, it is estimated that at least one in five septic systems malfunction annually (USEPA, 2002b) and septic system failure has been attributed to a combination of factors including age, poor design, lack of maintenance or local environmental conditions (Carroll et al., 2006). Septic systems recharging unprotected aquifers have been

shown to impair groundwater quality, and this is evidenced by the wide range of PPCPs detected in groundwater of regions heavily dependent on septic systems (Swartz et al., 2006; Conn et al., 2006; Godfrey et al., 2007; Schaider et al., 2014; 2016). The occurrence and levels of PPCPs in groundwater affected by septic systems is discussed in detail in section 2.4.

1.4 Effects of Exposure to PPCPs on Human Health

Several studies have established an association between environmental exposure to PPCPs and undesirable human health outcomes. For example, exposure to PPCPs with endocrine activities has been associated with higher breast cancer risks (Rudel et al., 1998) and other hormonally related cancers (US EPA, 1997). In addition, it is believed that long term exposure to PPCPs may also affect fertility (US EPA, 1997) and may trigger adverse effects on development and reproduction in both humans and wildlife (Campbell et al., 2006). Other risk factors include environmental exposure to antibiotics which has the potential to promote antibiotic resistant pathogens (Bengtsson-Palme & Larsson, 2016); antibiotic resistance results in the ineffectiveness of some antibiotics to treat infections and this potentially threatens human health on a global scale (World Health Organization, 2014). In recent years, human health risk of exposure to PPCPs through contaminated drinking water has received considerable attention (Schwab et al., 2005; Cunningham et al., 2010); however, there seems to be a huge uncertainty about the level of risk associated with PPCP occurrence in drinking water and what levels may be considered significant from the human health perspective (Bull et al., 2011). The extent of risks from exposure to PPCPs remain poorly characterized as the number of PPCP detections in the environment continues to grow (Diamond et al., 2011). Nevertheless, exposure to PPCPs through drinking water remains a risk factor, particularly in countries like Nigeria, where, domestic water wells are often located at unsafe distances (<30 m) from septic systems and water pumped from these drinking water supplies is consumed without treatment.

Research on PPCP occurrence and risk has been focused on Europe, North America and parts of Asia, notably China (Wilkinson et al., 2018). This regional bias has resulted in poorly characterized occurrence levels and effects of PPCPs in many developing regions, particularly the African region (Hughes et al., 2013).There is therefore an urgent need to expand PPCP research to developing countries as these countries continue to experience exponential growth in population and with the concomitant increase in disease burden, often exacerbated by inadequate health care infrastructure (Kookana et al., 2014), the tendency to expand and increase pharmaceutical use is imminent although precise quantities consumed by the population in such countries are often not available (World Health Organization., 2004).

1.5 Aims of the Thesis

It is crucial that we understand the impact of traditional septic systems on drinking water supplies in Nigeria. The overall aim of the PhD research was therefore to characterize the occurrence and levels of PPCPs in groundwater used for drinking water in southern Nigeria and assess the potential human health risk of exposure to PPCPs through drinking water intake in non-sewered communities. So far, there is a huge knowledge gap regarding exposure to PPCPs in Nigeria and many other developing countries as PPCP research continues to focus on developed countries.

The specific objectives were to:

1. Review the current knowledge regarding the occurrence and fate of emerging contaminants in septic systems and groundwater impacted by septic systems (Chapter 2)

2. Conduct a household survey to determine the most commonly used pharmaceuticals and personal care products in Nigerian households (Chapter 3)

3. Prioritize pharmaceuticals and personal care products in use based on their potential to enter groundwater from septic systems (Chapter 4)

4. Monitor drinking water supplies to characterize the occurrence and levels of PPCPs in groundwater impacted by septic systems (Chapter 5)

5. Assess the potential risk of indirect exposure to pharmaceuticals in drinking water (Chapter 6).

The information presented in the following chapters will be used to guide future groundwater monitoring campaigns in Nigeria and will allow a more accurate assessment of human health risk associated with exposure to PPCPs in drinking water supplies.

1.6 Thesis Overview

The thesis comprises 8 chapters. A brief description of each chapter is given below:

Chapter 1 of the thesis provides an introduction and purpose of the research and outlines the thesis structure.

Chapter 2 synthesises the existing knowledge on the occurrence and fate of pharmaceuticals in septic effluent and groundwater impacted by septic systems. This chapter attempts to identify the gaps in our current knowledge regarding the vulnerability of groundwater to onsite wastewater treatment systems regarding emerging contaminants, notably PPCPs.

Chapter 3 describes the development and implementation of questionnaire for household survey of PPCP use and disposal practices in Nigeria. The questionnaire was designed to quantitatively estimate PPCP use as a surrogate for the lack of PPCP usage data in Nigeria, and to determine household Willingness to Pay for proposed groundwater protection programs.

Chapter 4 describes the development and implementation of a risk-based prioritization approach for PPCPs entering groundwater from septic systems in Nigeria. The approach was applied to 41 most commonly used PPCPs in Nigeria, identified from the household usage survey described in chapter 3.

Chapter 5 explores the occurrence of a select group of 61 pharmaceutical compounds and 1 household insecticide (dichlorvos) in groundwater samples collected from domestic water supply wells located downgradient of septic systems in southern Nigeria. Pharmaceuticals were determined using highly sensitive High-Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/MS) method; dichlorvos was extracted from water samples by solid phase extraction (SPE) and determined by Gas Chromatography - Mass Spectrometry (GC-MS) method. The results were compared to previously reported occurrence data in the literature to determine any similarities or differences in usage patterns across various countries.

Chapter 6 describes the application of the derived Acceptable Daily Exposure (ADE) limit values for the assessment of risk from indirect exposure to pharmaceuticals from drinking water intake. The approach applied the ADE limit values to 29 pharmaceutical compounds detected in groundwater used for drinking water supply in Nigeria.

Chapter 7 highlights and discusses the main findings of the thesis. The broader implications of the reported results and recommendations for future research are also presented.

Chapter 2

A Review on the Occurrence and Fate of Emerging Organic Contaminants in Septic Systems and Downgradient Groundwater

2.1 Introduction

In recent years, several studies have observed emerging organic contaminants (EOCs) belonging to diverse chemical classes in domestic wastewater, where the potential exists for their onward release into the environment, either from WWTPs or septic systems (Conn et al., 2010; Lowe et al., 2007; Carrara et al., 2008; Kolpin et al., 2002). Conventional wastewater treatment typically does not remove all wastewater borne contaminants, and as such, EOC total load released into the environment is sometimes as high as the levels (e.g. several micrograms-per-liter range) measured in untreated wastewater (Ternes et al.,1999). To date, effluent quality from WWTPs particularly for EOCs has been better characterized than effluent quality from septic systems (Du et al., 2014) and studies on the behavior and fate of EOCs during wastewater treatment have been conducted more extensively in WWTPs (Ternes, 1998; Garcia et al., 2013; Baker & Kasprzyk-Hordern, 2013; Margot et al., 2015) than in septic systems (Du et al., 2014; Conn et al., 2006; Barnes et al., 2008).

Nonetheless, septic systems remain a crucial part of the global wastewater treatment infrastructure (USEPA, 2002b), and although their first use dates back to the 1800s (Swartz et al., 2006), the reliance on septic systems has increased over the last decades, with an estimated 500 million septic systems in global use (Conn et al., 2006). This figure is expected to rise in future, considering that even in advanced nations, household units in newly developed areas have fewer chances of being connected to centralized sewer systems, and consequently, are more likely to require decentralized sewage treatment (Carroll et al., 2006).

In the United States for example, approximately 25% of the population and about one-third of new housing developments in the urban fringes, treat and disperse domestic wastewater using septic systems (Lowe et al., 2009). In Australia, over 20% of residential wastewater is treated and dispersed using septic systems (Carroll et al., 2006; Beal et al., 2005), and about half a million households in Ireland rely on septic systems for sewage treatment (Keegan et al., 2014). In the highly populated low-income countries, septic system use is more prevalent (>80%) as sewer connectivity in both rural and urban areas is very low or non-existent (Kookana et al., 2014).

Despite the historic significance and relevance of septic systems in global wastewater treatment, there are growing concerns regarding potential environmental and public health risks associated with septic system use (Carrara et al., 2008; Keegan et al., 2014; Reilly et al., 2015;). In the past, issues about the quality of effluent from septic systems were focused on the presence of conventional wastewater pollutants, particularly pathogens, oxygen demanding wastes and nutrient chemicals with well documented adverse effects on human health and the environment (Conn & Siegrist, 2009). However, in recent times, one of the critical issues surrounding septic system use is the potential for EOCs, now frequently detected in wastewater to migrate from septic systems to the surrounding soil environment, unprotected aquifer and nearby surface waters (Reilly et al., 2015; Keegan et al., 2014; Carrara et al., 2008).

The impact of septic systems on unprotected aquifers has been demonstrated through various field studies linking the presence of a variety of EOCs (e.g. household chemicals, active pharmaceutical ingredients (APIs), endocrine active substances) in groundwater to nearby septic systems (Borchardt et al., 2003; Beal et al., 2005a; Bremer & Harter 2012; Keegan et al., 2014; Reilly et al., 2015; Borchardt et al., 2003; Mbuligwe, 2004; Carroll et al., 2004; Carroll et al., 2006; Conn et al., 2006). The following sections outline the decentralized approach to wastewater treatment using conventional septic systems and the sources and typical concentrations of a wide range of EOCs (including PPCPs, lifestyle and industrial compounds, various household

chemicals, biocides and pesticides), in septic systems and groundwater downgradient of septic systems, with focus on literature implicating septic systems as the major source of groundwater contamination. The fate of EOCs, including the dominant mechanisms governing their behavior in septic systems and in the subsurface environment is discussed.

2.2 Septic System Design, Function and Treatment

The decentralized approach to wastewater treatment is a modular system approach, which combines a variety of treatment modules, selected based on a number of different considerations, such as treatment efficiency needs (e.g. discharge or reuse), affordability, land availability, volume and quality of wastewater and legal effluent requirements (Reuter et al., 2009). Onsite systems can treat domestic wastewater using various technical configurations, including the use of sedimentation ponds, settlers, septic tanks, Imhoff tanks or biodigester for primary treatment and/or the use of baffled reactors or fixed-bed filters for secondary anaerobic treatment (Beal et al., 2005; Reuter et al., 2009).

The ultimate goal during onsite sewage treatment is to remove contaminants from wastewater and produce a treated effluent with reduced potential to contaminate local water resources including groundwater, drinking water wells and nearby streams and lakes (Lowe et al., 2007). This is important given that the dispersal mechanism for onsite systems relies on the continuous discharge of partially treated wastewater within the immediate soil environment (Subedi et al., 2014), a dispersal mechanism which allows a consistent flow of discharges likely to increase the loading rate of contaminants in the soil treatment area and consequently may increase the risk of contamination of downgradient groundwater and/or hydraulically-connected surface water which may be used as a drinking water source (Conn et al., 2006; Teerlink et al., 2012). Adequate removal of contaminants during onsite wastewater treatment is therefore essential to protect water quality and public health (Conn & Siegrist, 2009; Toor et al., 2014).

2.2.1 Basis of Sewage Treatment in a Conventional Septic Tank System

The conventional septic tank system (STS) (Fig 2.1; adopted from Schaider et al. 2017) consists primarily of i) a septic tank, which is a watertight settling chamber made of pre-cast or cast-in-place concrete, fiber glass or polyethylene, located below ground level to receive household wastewater for primary treatment; ii) a septic effluent absorption system, which is a system of dispersal units, made up of subsurface soakaway or seepage pit, partially filled with aggregates and iii) a soil treatment unit – which is the soil profile or vadose zone that lies beneath the soakaway or seepage pit (Del Rosario et al., 2014; Siegrist et al., 2012).

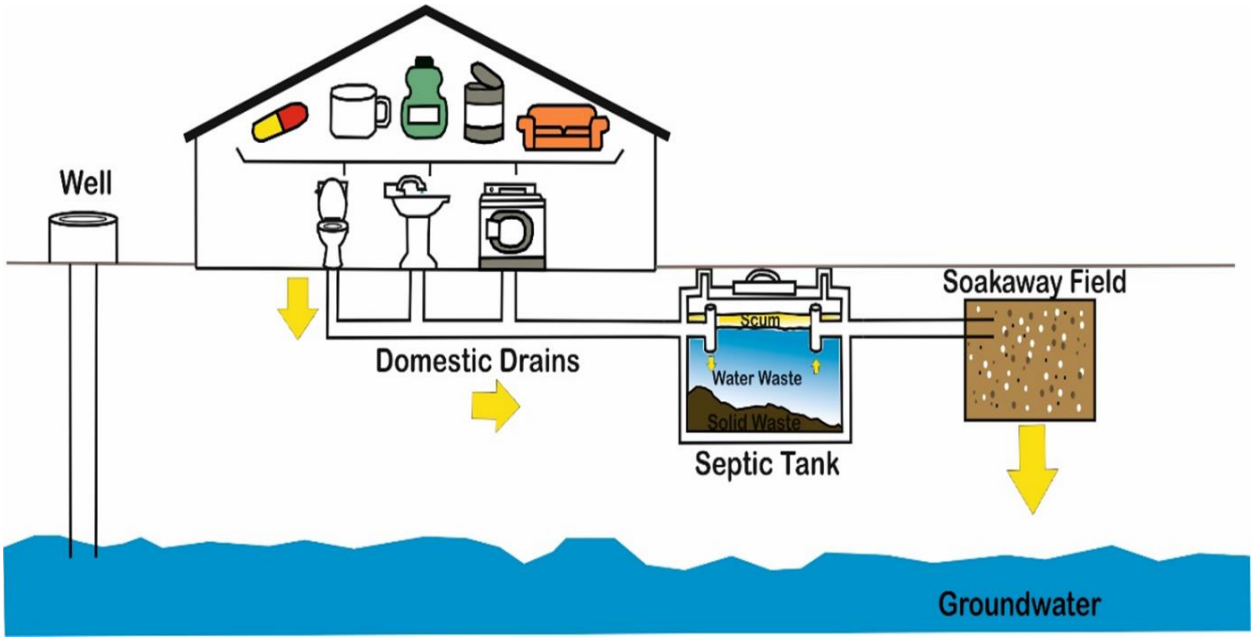


Figure 2. 1 Schematic of a Conventional Septic Tank System

The STS is designed to provide basic level treatment of domestic wastewater (Conn et al., 2006), which depending on the source, is differentiated into black-water (wastewater from the toilet comprising mainly urine and feces) and grey-water (wastewater from sinks, bathtub and laundry).

Unlike municipal WWTPs which are strategically designed to receive wastewater from a large number (thousands to hundreds of thousands) of households across a population, wastewater discharged into septic systems come from single sources, arising principally from individual households or a cluster of households and also from nonresidential sources including businesses, commercial buildings and institutions (Schaider et al., 2013; Conn & Siegrist, 2009). Treatment functions of the STS, which involves primary and secondary treatment of wastewater are summarized below (USEPA, 2002):

2.2.2 Primary Treatment of Domestic Wastewater in the Conventional Septic Tank System

The STS relies on gravity to transport household wastewater to the septic tank and to move septic effluent from the septic tank to the subsurface absorption field, usually through a distribution box or a dosing tank. The septic tank as a confined primary treatment unit relies on physical and biological processes to reduce the typical constituents of domestic wastewater, including oil & grease, fats and settleable solids to partially treated wastewater. Wastewater flowing from the house through sewer pipes enters the septic tank, where materials heavier than water (heavy solids) settle to the bottom of the tank and are subsequently, slowly and partially decomposed by anaerobic bacteria to form sludge and biogases (predominantly methane). Materials lighter than water (light solids and grease) rise to the surface to form a scum layer. In between the sludge and scum layer, is a partially treated wastewater which is eventually discharged as liquid effluent through a dosing tank or exit pipe into the subsurface disposal system for secondary treatment.

2.2.3 Secondary Treatment of Domestic Wastewater in the Subsurface Soil Absorption Field

The subsurface soil absorption field represents the secondary treatment unit of a conventional septic tank system and is conventionally called a drain field (or leach field). The soil absorption unit consists of infiltration trenches or soakaway or seepage pit, which in turn consist of a layer of clean gravel or crushed stone. As the pre- treated effluent septic tank effluent (STE) percolates through the soil matrix or vadose zone, minute solids, some nutrients, harmful bacteria and other pathogens are removed by filtration, biochemical reaction and further decomposition by microorganisms present in the soil and through these processes, contaminants are reduced considerably from the STE. Hence, a functional drain field can potentially safeguard local water supplies (surface and groundwater resources) from microbiological and chemical contamination through natural disinfection (USEPA, 2002). However, to achieve functionality, homeowners operating septic systems must follow stipulated guidelines, especially pertaining to design, construction, operation, maintenance and management of the system (Lowe et al., 2007).

2.3 Sources of EOCs in Septic Systems and Downgradient Groundwater

A wide range of chemicals produced each year are incorporated into various household products used daily to satisfy among others, the need for personal care, sanitation and hygiene and improved health and wellbeing (Boxall et al., 2012; Margot et al., 2015). Once used, most of these chemicals eventually end up in septic systems or sewers as constituents of domestic wastewater. Toor et al. (2014) characterized consumer product chemicals into four broad categories which include: 1) pharmaceuticals, comprising drugs and drug byproducts, excreted intact or as biologically metabolized drugs in feces and urine (Conn & Siegrist, 2009) or directly disposed of into the drains as unused or expired medications (Bound & Voulvoulis, 2005); 2) home use chemicals such as surfactants (found in detergents, dishwashing liquids and soaps),

antimicrobial agents (present in soap and toothpaste), stimulants (e.g. caffeine and nicotine); 3) pesticides (such as the insect repellent DEET) which are washed off after application on our skin, clothes or other household surfaces and 4) Volatile organic compounds (VOCs) which are found in many consumer products such as solvents, paints and thinners, adhesives, wood preservatives and air fresheners. A range of other chemicals used daily in homes (such as fragrances, food and beverage additives, preservatives, anti-corrosives, chelating agents) or contained in household equipment (such as plasticizers and plastic additives, flame retardants, per fluorinated compounds) often end up in septic systems as constituents of wastewater (Margot et al., 2015).

Various factors determine the overall composition and characteristics of domestic wastewater including: (i) wastewater source characteristics (e.g. residential or nonresidential sources), (ii) water use and conservation practices contributing to the wastewater volume and flow; (iii) usage and disposal pattern of consumer product chemicals; (iv) health condition of residents (which determines drug consumption); (v) number and age of occupants in a household; and (vi) geographical setting (Toor et al., 2014; Conn et al., 2006; Schaider et al., 2013; Conn & Siegrist, 2009). The importance of geographical setting as a determining factor of wastewater composition and ultimately exposure relate to the regional differences in consumption patterns for domestic products, driven by prescription practices, pharmaceutical costs, disease pressures and / or existence of marketing authorization of products (Burns et al., 2018). For example, regarding diseased pressure, while antimalarial agents are expected to be constituents of domestic wastewater in tropical regions, such medicines would be less frequently characterized in wastewater from temperate regions where malaria is non-endemic. Concerning the existence of marketing authorization, the United States for example has since the early 1990s curtailed the use of dichlorvos, a household insecticide (EPA, n.d.) and the European Union (EU) has banned its use in EU countries following reports on its acute toxicity; by contrast, dichlorvos is recommended for use in many developing countries where it is extensively applied to control household pests, particularly mosquitoes to prevent or reduce the incidence of malaria); the wider

implication is that the environmental emission of dichlorvos will be a priority in developing countries than in developed countries where there is restricted use.

The human health effects of exposure to EOCs through drinking water intake remain largely unknown (Margot et al., 2015; Schaider et al., 2017), although emergence of antimicrobial resistance in pathogens due to antimicrobial exposure in environment is considered an actual risk and has been widely reported (Bengtsson-Palme & Larsson, 2016; Holmes et al., 2016; Parthasarathy et al., 2018). Knowledge of the occurrence, typical concentrations and fate of EOCs in septic systems and downgradient groundwater is necessary for characterizing septic system contamination potential of drinking water supplies as discussed below.

2.4 Occurrence and Concentrations of EOCs in Septic Systems and Downgradient Groundwater

The occurrence of a wide range of EOCs in groundwater recharged by septic systems, albeit in trace levels (ng/L to µg/L levels) indicates that most compounds may be poorly removed during treatment in septic systems (Hinkle et al., 2005) and underscores their migratory potential and persistence during subsurface transport (Godfrey et al., 2007). The goal of this section was to characterize the pollution risk of septic systems to the underlying groundwater and adjacent drinking water wells, regarding EOC occurrence and levels. To address this goal, information was sought from scientific journals and published reports through a systematic literature search of the Web of Science ™ and Scopus databases, as well as Google Scholar search engine. The search was made with the following combinations of keywords or search terms: ‘onsite wastewater treatment systems,’ or ‘septic systems,’ or ‘septic tank system,’ or ‘soil absorption system,’ or ‘onsite systems,’ or ‘seepage pits,’ or ‘drainfield,’ or ‘leach field’ with either ‘organic wastewater contaminants,’ or ‘pharmaceuticals,’ or personal care products,’ or ‘emerging contaminants,’ or ‘emerging organic contaminants,’ or ‘micropollutants’. The bibliographies of identified articles of interest also provided additional targeted search. Articles of interest were those that provided

information on effluent concentrations of EOCs in onsite wastewater (i.e. septic tank effluent) and/or EOC concentrations in underlying aquifers (or domestic and public water supply wells) in unsewered communities and have largely implicated septic systems as the sole or major contributor of EOCs to groundwater and / or drinking water wells. In total, 20 studies fitting these criteria were identified, all of which were conducted in North America (i.e. the United states and Canada). Most of the studies were conducted at various locations in the United States and only three locations were reported for the Canadian study. One issue that occurred during the literature search was the non-uniformity in reporting limits for EOCs across studies. The inconsistencies in reporting limits may be attributed to the different sensitivities of the analytical instruments used by various authors. Because comparing data in different units can be both difficult and misleading, all data values reported in parts per billion (i.e. µg/L) were converted to parts per trillion (i.e. ng/L) by multiplying the values by a factor of 1000. The literature search revealed the occurrence of a total of 97 EOCs and metabolites in STE samples and 109 EOCs and metabolites in groundwater samples reported in the various studies and the full breakdown of the occurrence and concentrations of all EOCs in STE and groundwater is summarized in the Appendix in Table A.A1 and Table A.A2, respectively. EOCs in the current review have been divided into six broad categories: pharmaceuticals, life style compounds, industrial compounds, steroids and hormones, personal care products and food additives. Due to the limited availability of relevant literature, compounds reported in four or more case studies were categorized as frequently occurring compounds in the current review. Summary statistics for the lowest, average and highest maximum concentrations found in STE and groundwater for individual EOCs are presented in Table 2.1 and Table 2.2, respectively. Average maximum concentrations (i.e. sum of maximum concentrations reported for each EOC divided by the number of case studies) for the most commonly detected compounds in STE and groundwater were reported in the range 450 - 9.3 x 10^6 ng/L and 100 - 8.4 x 10^4 ng/L respectively. The seven most frequently reported compounds in both STE and groundwater were: ibuprofen (STE 6 studies, average max. conc. = 3.5 x 10^4 ng/L;

groundwater 4 studies, average max. conc. = 1.8 x 10^3 ng/L); carbamazepine (5, 113 ng/L; 4, 89 ng/L); sulfamethoxazole (5, 3.2 x 10^4 ng/L; 7, 306 ng/l); trimethoprim (6, 1.6 x 10^4 ng/L; 6, 104 ng/L); caffeine (10, 1.1 x 10^6 ng/L; 7, 829 ng/L); 1,7-dimethylxanthine (6, 2.1 x 10^5 ng/L; 4, 723 ng/L) and 4-nonylphenol (8, 1.7 x 10^5 ng/L; 4, 2.1 x 10^4 ng/L). Triclosan (6, 3.7 x 10^4 ng/L); acetaminophen (5, 3.7 x 10^5) and ethylenediaminetetraacetic acid (EDTA) (5, 1.7 x 10^6 ng/L) were reported to occur frequently in STE but were reported less frequently (n < 4) in groundwater. Gemfibrozil (4, 645 ng/L) and tris (2-chloroethyl) phosphate (TCEP), (4, 100 ng/L) occurred frequently in groundwater but were reported less frequently in STE.

2.4.1 Pharmaceuticals

Pharmaceuticals belong to a wide range of medicinal compound groups and following patient use, active pharmaceutical ingredients (APIs) become part of the domestic waste stream primarily via human excretion (in urine and feces) and / or through the disposal of unused and expired medicines (Ruhoy and Daughton, 2007; Daughton, 2003; Daughton and Ruhoy, 2009). Pharmaceutical residues (APIs) end up in the environment through the discharge of untreated or partially treated wastewater to wastewater receiving environments such as surface water and groundwater resources (Kolpin et al., 2002; Lapworth et al., 2012). The dominant group of pharmaceutical compounds (e.g. antibiotics, antiepileptics and anti-inflammatory drugs) often associated with wastewater treatment processes (Drewes et al., 2002; Monteiro & Boxall, 2010) were also the most frequently reported compounds in STE (n = 6) and groundwater (n = 4) in this review. In STE, sulfamethoxazole (antibiotic), trimethoprim (antibiotic), acetaminophen (analgesic), ibuprofen (anti-inflammatory) and carbamazepine (antiepileptic) were reported in at least four studies in the United States and Canada (Table 2.1).

Table 2.1 Summary of Lowest, Average and Highest Maximum EOC concentrations (ng/L) in Septic Tank Effluent Reported in at least 4 Separate Studies and their Major Use

Compound	n	Lowest	Average	Highest	Use
Pharmaceuticals					
Acetaminophen	5	45000	374640	1,530,000	Analgesic
Ibuprofen	6	40	35220	110,000	Anti-inflammatory
Carbamazepine	5	2.04	113	450	Antiepileptic
Sulfamethoxazole	5	40	32700	64,000	Antibiotic
Trimethoprim	6	4.77	16999	100,000	Antibiotic
Personal Care Products					
Triclosan	7	200	37973	82,000	Antimicrobial
Life Style Compounds					
Caffeine	10	10000	1060164	9,300,000	Stimulant
1,7-Dimethylxanthine	6	10000	216500	1,010,000	Caffeine metabolite
Industrial compounds					
4-Nonyphenol[a]	8	6100	174513	650,000	Surfactant metabolite
EDTA	5	34000	383100	1,700,000	Metal chelating agent

n=number of studies; a=Degradate; EDTA=Ethylenediamine tetra acetic acid; Average calculated from the maximum concentrations reported for each compound in different case studies

Table 2.2 Summary of Lowest, Average and Highest Maximum EOC concentrations (ng/L) in groundwater downgradient of septic systems Reported in at least 4 Separate Studies and their Major Use

Compound	n	Lowest	Average	Highest	Use
Pharmaceuticals					
Ibuprofen	4	40	1857	6800	Anti-inflammatory
Carbamazepine	4	10	89	210	Antiepileptic
Sulfamethoxazole	7	40	306	1330	Antibiotic
Trimethoprim	6	1.0	104	580	Antibiotic
Gemfibrozil	4	1.2	645	1950	Antilipemic
Personal Care Products					
DEET	6	6.0	242	800	Insect repellant
Life Style Compounds					
Caffeine	7	120	829	1710	Stimulant
1,7-Dimethylxanthine[a]	4	22	723	1730	Caffeine metabolite
Industrial compounds					
4-Nonyphenol[a,]	4	20	21780	84,000	Surfactant metabolite
TCEP	4	13	43	100	Flame retardant

n=number of studies; a=Degradate; DEET = N,N-diethyl-meta-toluamide; TCEP = Tris(2-carboxyethyl)phosphine; Average calculated from the maximum concentrations reported in different case studies for each EOC.

Interestingly, four of these compounds ibuprofen, carbamazepine, sulfamethoxazole and trimethoprim were also the most frequently observed compounds in groundwater down gradient of septic systems (Table 2.2). The co-occurrence of these compounds in STE and down gradient groundwater confirms claims in earlier studies that groundwater downgradient of septic systems may be vulnerable to septic system leachates (Hinkle et al., 2005). Table 2.3 and Table 2.4 provide an overview of the concentration of EOCs in downgradient groundwater and in STE, respectively, reported in various studies, including country and sampling locations where available.

2.4.1.1 Analgesics and Anti-inflammatories

Analgesics are pain relief medicines and nonsteroidal anti-inflammatory drugs (NSAID) are used to relieve pain and to suppress inflammation. Several active substances belong to this therapeutic subgroup including acetaminophen, acetylsalicylic acid (aspirin), ibuprofen, naproxen, ketoprofen, diclofenac, fenoprofen, indomethacin, tramadol and codeine (opioid analgesic). Some of these pharmaceuticals have been widely detected in STE and groundwater downgradient of septic systems in the United States and Canada. Acetaminophen was the most frequently detected (n = 5) analgesic in STE and ibuprofen was the prevalent anti-inflammatory drug in both STE (n = 6) and groundwater (n = 4) across the United States and Canada. In a review by Monteiro & Boxall (2010), acetaminophen and ibuprofen were among the most widely detected compounds in sewage treatment plant effluents and surface waters in the United States, Canada and Europe. According to Luo et al. (2014), the widespread environmental occurrence of pharmaceuticals may reflect local production and consumption patterns within a particular region. Other analgesics and anti-inflammatories detected in groundwater, though less frequently (n < 4) include diclofenac, ketoprofen, indomethacin, naproxen, salicylic acid and codeine (Conn et al., 2010; Carrara et al., 2008; Hinkle et al., 2005; Godfrey et al., 2007; Verstraeten et al., 2005). In the United States, diclofenac and ketoprofen concentrations in single family septic tanks were

<100 ng/L but naproxen concentrations were as high as 1.5 x 10^5 ng/L in STE in the same study (Conn et al., 2010). In Ontario Canada, ketoprofen and fenoprofen were not detected in STE but ketoprofen concentration was found in groundwater in the range <3 to 30 ng/L; diclofenac was not detected in STE, but it was found in groundwater from two campsites at 20 ng/L and 30 ng/L, respectively. A much higher concentration (5580 ng/L) was reported for indomethacin detected up to 10 meters downgradient of an infiltration bed (Carrara et al., 2008). Codeine concentration as high as 10^5 ng/L was reported in a high school septic tank in Montana, USA (Godfrey et al., 2007) but studies reporting its occurrence in groundwater have observed much lower concentrations in groundwater from La Pine, Oregon (20 ng/L) (Hinkle et al., 2005) and Nebraska shallow wells (80 ng/L) (Verstraeten et al., 2005). Salicylic acid levels in STE from Canada was up to 480 ng/L and observed levels in groundwater samples from three sites in the same study, ranged from <4 to 480 ng/L (Carrara et al., 2008). According to the authors, these levels were comparable to those observed in untreated and partially treated wastewater from Canadian municipal wastewater treatment works (Carrara et al., 2008). They also found salicylic acid to show high migratory potential as it was observed at a distance as far as 20 m downgradient of an infiltration bed. In the United States, salicylic acid was observed at STE from single family homes at a concentration range of 100 to 2.1 x 10^5 ng/L. Conn et al. (2010) associated the high occurrence of salicylic acid in STE to its widespread use in non-prescription drugs, its release into wastewater by the breakdown of other drugs such as aspirin (acetyl salicylic acid) and mesalamine during wastewater treatment and its wide application as an additive in cosmetics and other personal care products. Naproxen was observed over 20 m along the horizontal length of an aquifer in Canada (Carrara et al., 2008). The mobility potential of naproxen was explained in a recent study involving a kinetic batch experiment to determine pharmaceutical attenuation in water-soil systems; the authors found naproxen to be poorly retained in soils (Martinez-Hernandez et al., 2016) and this may its migratory potential in the subsurface. Some analgesics and anti-inflammatory drugs were reported less frequently (n < 4) in groundwater and include

acetaminophen (Verstraeten et al., 2005), celecoxib and tramadol (Phillips et al., 2015). Hydrocodone (narcotic analgesic) and antipyrine (analgesic for ear infections) were not detected in STE from Montana, USA (Godfrey et al., 2007) but recent studies in Cape Cod, Massachusetts reported for the first time, the occurrence of antipyrine in drinking water supply wells (Schaider et al., 2014; 2016).

2.4.1.2 Beta-Blockers

Beta-blockers are medicines used to treat a wide range of conditions including angina, arrhythmia, high blood pressure and anxiety and consequently, are among the most commonly prescribed pharmaceutical compounds. Despite their wide-spread use, atenolol was the only beta-blocker detected in STE and groundwater in the United States. In Skaneateles Lake, New York, atenolol concentrations in effluents from septic tanks ranged from 0.4 to 506 ng/L (Subedi et al., 2014). In Cape Cod, Massachusetts, atenolol was detected at trace concentration (0.8 ng/L) in one out of twenty public drinking water supply wells tested for a wide range of pharmaceuticals and organic wastewater contaminants (Schaider et al., 2014). Although atenolol was not frequently detected in groundwater ($n < 4$) in this study, it has been one of the most frequently detected compounds in surface water and finished drinking water screened for pharmaceuticals and hormonally active compounds in the United States (Benotti et al., 2009); as a consequence of its frequent occurrence in source and finished water, atenolol has been suggested as a potential indicator for wastewater contamination of natural source waters (Benotti et al., 2009). Atenolol has also been considered to be a potential priority substance following a prioritization study which found atenolol to be a highly consumed compound, as well as being toxic and persistent during wastewater treatment (Schaider et al., 2014).

Table 2. 3 Reported data on concentrations of EOCs (ng/L) in groundwater downgradient of septic systems in the United States and Canada

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Pharmaceuticals			
Analgesics & Anti-inflammatories			
Acetaminophen	15 - 120	USA (Oregon & Nebraska)	5, 7
Diclofenac	Nd - 30	Canada (Point Pelee- & Lake Joseph)	1
Ibuprofen	Nd - 12000	USA (Cape Cod-Massachusetts, Oregon, Nebraska & North Carolina) Canada (Ontario)	1, 5, 7, 9
Ketoprofen	Nd - 30	Canada (Ontario)	1
Naproxen	Nd - 5580	Canada (Ontario)	1
Salicylic acid	4 - 480	USA (Cape Cod-Massachusetts); Canada (Point Pelee- & Lake Joseph)	1, 12
Antipyrine	1.0 – 2.0	USA (Cape Cod-Massachusetts)	6, 12
Diclofenac	Nd - 30	Canada (Point Pelee- & Lake Joseph)	1
Indomethacin	Nd - 20	Canada (Ontario)	1
Codeine	20 - 80	USA (Oregon & Nebraska)	5, 7
Celecoxib	>100[g]	USA (New England)	8
Tramadol	>100[g]	USA (New England)	8
Antibiotics			
Erythromycin-H2O	750	USA (Nebraska)	7
Sulfamethoxazole	<RL- 1330	USA (Cape Cod-Massachusetts, Oregon, Nebraska, Montana, New England & Florida)	3, 5, 6, 7, 8, 10, 12
Sulfachloropyridazine	0.7	USA (Cape Cod-Massachusetts)	12
Sulfamethizole	1.0	USA (Cape Cod-Massachusetts)	6
Sulfathiazole	0.2	USA (Cape Cod-Massachusetts)	12
Trimethoprim	0.7 - 580	USA (Cape Cod-Massachusetts, Oregon, Nebraska, Montana & Washington)	3, 5, 6, 7, 11, 12
Ciprofloxacin	50	USA (Nebraska)	7
Enrofloxacin	50	USA (Nebraska)	7
Sarafloxacin	50	USA (Nebraska)	7

Table 2.3 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Beta Blockers			
Atenolol	0.8	USA (Cape Cod-Massachusetts)	6
Lipid Regulators			
Gemfibrozil	Nd - 1950	USA (Cape Cod-Massachusetts; La Pine Oregon, Canada (Ontario)	1, 5, 6, 12
Bezafibrate	Nd - 350	Canada (Long Point & Lake Joseph, Ontario)	1
Clofibric acid	Nd - 15	Canada (Lake Joseph, Point Pelee & Long Point, Ontario)	1
Simvastatin	14	USA (Cape Cod-Massachusetts)	12
Antiepileptics			
Carbamazepine	10 - 210	USA (Cape Cod-Massachusetts, Oregon, Missoula city, Montana)	3, 5, 6, 12
Phenytoin	66 - 100	USA (Cape Cod-Massachusetts & New England)	6, 8
Primidone	9.0	USA (Cape Cod-Massachusetts)	12
Steroids and Hormones			
Estrone(E1)	BDL - 120	USA (Cape Cod-Massachusetts & New York)	2 , 8
17β-estradiol (E2)	BDL-45	USA (Cape Cod-Massachusetts)	2
Estriol (E3)	2.5	USA (New York)	8
Estrone 3-sulphate (E1-3S)	1.0 - 4.0	USA (Cape Cod-Massachusetts)	2
Cis-testosterone	0.04	USA (Cape Cod-Massachusetts)	12
Progesterone	0.02	USA (Cape Cod-Massachusetts)	12
Cholesterol	BDL - 3500	USA (Colorado & La Pine, Oregon)	4, 5
Coprostanol	10000	USA (Colorado)	4
Anthelmintic			
Thiabendazole	<RL	USA (La Pine Oregon)	5
Antihistamine			
Cimetidine	<RL	USA (La Pine, Oregon)	5
Ranitidine	<RL	USA (La Pine, Oregon)	5
Diphenhydramine	<RL	USA (La Pine ,Oregon)	5

Table 2.3 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Calcium Channel Blockers (Antihypertensives)			
Diltiazem	<RL	USA (La Pine ,Oregon	5
Dehydro nifedipine (nifedipine metabolite)	<RL - 20.0	USA (La Pine ,Oregon, Nebraska)	5, 7
Antiasthmatic			
Salbutamol	<RL	USA (La Pine ,Oregon)	5
Anticoagulants			
Warfarin	<RL - 10.0	USA (La Pine ,Oregon, Nebraska)	5 , 7
Anxiolytics			
Meprobamate	2.0 - 100	USA (Cape Cod, Massachusetts; New England)	6, 12, 8
Antifungals			
Fluconazole	>100	USA (New England)	8
Barbiturates			
Butalbital	>100	USA (New England)	8
Phenobarbital	>100	USA (New England)	8
Carisoprodol	>100	USA (New England)	8
Anesthetics			
Lidocaine	100 - 500	USA (New England)	8
Life style compounds			
Stimulant			
Nicotine	<25 - 50	USA (Frenchtown /Missoula City Montana)	3
Cotinine (Nicotine metabolite)	1.0 - 60	USA (Missoula city & Montana; Nebraska; Cape Cod Massachusetts)	3 ,7, 12
Caffeine	BDL - 1710	USA (Cape Cod, Massachusetts, Missoula City & Montana, Colorado, La Pine Oregon, Nebraska, Greenville North Carolina, Colorado, Woodville-Florida	2, 3 ,4 ,5, 7, 9, 10
1-7-dimethylxanthine (caffeine metabolite)	BDL-1730	USA (Cape Cod-Massachusetts, La Pine, Oregon, Nebraska, Woodville-Florida	2, 5, 7, 10
Personal Care Products			
Sunscreen			
Benzophenone	>100	USA (New York)	8

Table 2.3 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Personal Care Products			
Disinfectant			
Triclosan	<RL – 7.0	USA (Colorado), Canada (Ontario)	4,1
Musk Fragrance			
Galaxolide	<RL	USA (New York, Woodville-Florida)	8, 10
Tonalide	<RL	La Pine Oregon	5
Insect repellent			
DEET	BDL - 800	USA (La Pine, Oregon, Cape Cod, Massachusetts, New York, Greenville, North Carolina, Washington)	5, 6, 8, 9, 11, 12
Food Additives			
Acesulfame (Artificial sweetener)	5300	USA (Cape Cod, Massachusetts)	12
Triethyl citrate (Flavoring agent)	>100	USA (New York)	8
Antioxidants			
2[3]-t-Butyl-4-methoxyphenol	<RL	USA (Colorado)	4
2,6-Di-t-butyl-1,4- methylphenol	<RL	USA (Colorado)	4
Industrial compounds			
Detergents			
Surfactant metabolites			
4-nonylphenol	BDL - 84000	USA (Colorado), Canada (Ontario)	2, 4, 6, 8,
NP1EC	<RL - 35000	USA (Cape Cod, Massachusetts)	2, 14
NP2EC	4.4 - 69000	USA (Cape Cod, Massachusetts)	2
∑NPEO	<RL - 5000	USA (Cape Cod, Massachusetts, Colorado)	2, 4
∑NPEC	2400	USA (Cape Cod, Massachusetts	4
4-n-Octylphenol	<RL	USA (Colorado)	4
4-t-Octylphenol	<RL - 100	USA (New York, USA (Colorado)	8, 4
∑OPEO	<RL	USA (Colorado)	4
OP4EO	32900	USA (Cape Cod, Massachusetts)	14
4-Propylphenol	<RL	USA (Colorado)	4
4-t-Butylphenol	<RL	USA (Colorado)	4
4-Ethylphenol	<RL	USA (Colorado)	4
4-Methylphenol	530	USA (Colorado)	4

Table 2.3 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
4-t-Pentylphenol	<RL	USA (Colorado)	4
2,6-Di-t-butylphenol	<RL	USA (Colorado)	4
Surfactants			
DAS	BDL-4180	USA (Cape Cod)	2
DSBP	0.5-27	USA (Cape Cod)	2
MBAS	200000 - 10^6	USA (Cape Cod)	2
Metal complexing agents			
NTA	<RL	USA (Colorado)	4
EDTA	3800 - 44500	USA (Cape Cod, Colorado)	2, 4
Perfluoro surfactants			
PFOA	22	USA (Cape Cod, Massachusetts)	6
PFOS	97	USA (Cape Cod, Massachusetts)	6
PFBS	23	USA (Cape Cod, Massachusetts)	12
PFHpA	1.0	USA (Cape Cod, Massachusetts	12
PFHxA	41	USA (Cape Cod, Massachusetts	12
Disinfectants			
Phenol	<RL	USA (Woodville-Florida)	10
P-Cresol	2900	USA (Minnesota)	13
Flame Retardants & Plasticizers			
Flame retardants			
TCEP	BDL - 100	USA (Cape Cod, Massachusetts, La Pine Oregon, New York, Washington)	6, 5, 8, 11
TCPP	40	USA (Cape Cod, Massachusetts	6
TDCPP	BDL - 1000	USA (Cape Cod, Massachusetts, La Pine, Oregon, Woodville-Florida	6, 5, 10
TBP	11 - 1000	USA (La Pine Oregon, Cape Cod, Massachusetts)	5, 12
2-EHDP	15	USA (Cape Cod, Massachusetts)	12
Plasticizer			
TBEP	50 - 20000	USA (Cape Cod, New York & New England)	6, 8
TPP	14	USA (Cape Cod, Massachusetts)	12
Bisphenol A	<RL - 44	USA (Cape Cod, Massachusetts)	14

Table 2.3 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Fumigant			
1,2-dichlorobenzene	<RL	USA (Colorado)	4
1,3-dichlorobenzene	<RL	USA (Colorado)	4
Deodorizer			
1,4-dichlorobenzene	<RL	USA (Colorado)	4
Dry cleaning	<RL	USA (La Pine Oregon)	5
Tetrachloroethane	<RL	USA (Colorado)	4

1 - Carrara et al., (2008) **2** - Swartz et al., (2006) **3** - Godfrey et al., (2007) **4** - Conn & Siegrist, (2009) **5** - Hinkle et al., (2005) **6** - Schaider et al., (2014) **7** - Verstraeten et al., (2005) **8** - Phillips et al., (2015) **9** - Del Rosario et al., (2014) **10** - Katz et al., (2010) **11** - Dougherty et al., (2010) **12** - Schaider et al., (2016) **13** - Erickson et al., (2014); **PFBS** (Perfluoro butane sulfonic acid); **2-EHDP** (Ethyl hexyldiphenyl phosphate); **PFHpA** (Perfluoro heptanoic acid); **TBEP** (tris(2-butoxyethyl)phosphate; **TCEP** (tris(2-chloroethyl)phosphate; **TDCPP** (tris(1,3-dichloro-2-propyl)phosphate; **TBP** (Tributyl Phosphate); **TPP** (Triphenyl phosphate**); DEET** (N,N-diethyl-meta-toluamide); **PFOA** (perfluorooctanoic acid); **DAS** (2-disulfonate); **DSBP** (4,4-bis(2sulfostryl)biphenyl); **MBAS** (Methylene blue active substance); ∑**NPEO** (NP1EO - NP3EO); ∑**NPEC** (NP1EC - NP3EC); **DEET** (N,N-diethyl-meta-toluamide); **PFBS** (Perfluoro butane sulfonate; **PFOS** (Perfluoro octane sulfonate); **PFOSA** (Perfluoro octane sulfonate); **PFHxA** (Perfluoro hexanoic acid); **PFHPA** (Perfluoro heptanoic acid; **PFOA** (Perfluoro octanoic acid); **PFNA** (Perfluoro nonanoic acid); **PFDA** (Perfluoro decanoic acid; **PFUnDA** (Perfluoro undecanoic acid); **PFDoDA** (Perfluoro dodecanoic acid); **NTA** (Nitro acetic acid); **EDTA** (Ethylenediamine acetic acid); ∑**NPEC** (Sum of 4-nonylphenol mono-ethoxy carboxylate through 4-nonylphenol tetra-ethoxy carboxylate); ∑**NPEO** (Sum of 4-nonylphenol mono-ethoxylate through 4-nonylphenol tetra-ethoxylate); **OP4EO** (Octylphenol tetraethoxylate); ∑**OPEO** (Sum of 4-tert-octylphenolmonoethoxylate through 4-tert-octylphenoltetraethoxylate); **NP1EC** (4-Nonylphenolmonoethoxycarboxylate); **NP2EC** (4-Nonylphenoldiethoxycarboxylate); **NPEO** (Nonylphenol Ethoxylates); **NPEC** (Nonylphenol Ethoxy carboxylate); **TBEP** (tris (2-butoxyethyl) phosphate; **TPP** (Triphenyl phosphate); **TCEP** (tris(2-chloroethyl) phosphate; Nd (not detected); **<RL** (less than Reporting Limit); **BDL** (Below Detection Level); **ng^{-1}** (nanogram per liter)

Table 2. 4 Reported data on concentrations of EOCs (ng/L) in Septic Tank Effluent in the United States and Canada

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Pharmaceuticals			
Analgesics & Anti-inflammatories			
Acetaminophen	10^5 - 1530000	USA (La Pine, Oregon, Montana, Colorado, Woodville, Florida	5, 3, 4, 7, 14
Diclofenac	<RL	USA (Florida, Colorado, Minnesota)	6
Ibuprofen	<RL - 110000	USA (Cape Cod-Massachusetts, Oregon, Nebraska & North Carolina)	1, 5, 6, 10, 11, 15
Ketoprofen	<RL	USA (Florida, Colorado, Minnesota)	6
Naproxen	<RL - 150000	USA (Florida, Colorado, Minnesota)	6
Salicylic acid	Nd - 210000	USA (Florida, Colorado, Minnesota); Canada (Ontario)	1, 12
Diclofenac	<RL	USA (Florida, Colorado, Minnesota)	6
Indomethacin	Nd - 4	Canada (Ontario)	1
Codeine	66 - 10^5	USA (La Pine, Oregon; Montana)	5, 3
Antibiotics			
Erythromycin	Nd - 18000	USA (Montana, Colorado)	3, 7, 11
Erythromycin-H2O	200 - 320	USA (Colorado)	11
Sulfamethoxazole	<RL- 1330	USA (La Pine, Oregon, Montana, Woodville, Florida, Skaneateles Lake, New York)	5, 3, 4 , 14, 15
Tetracycline	20000	USA (Colorado)	7
Trimethoprim	<RL - 10^5	USA (La Pine, Oregon, Montana, Colorado, Skaneateles Lake, New York)	5, 3, 4, 7, 11, 15
Ciprofloxacin	36 - 593	USA (Colorado)	7
Norfloxacin	39 - 110	USA (Colorado)	7
Ofloxacin	18 - 960	USA (Colorado)	7
Azithromycin	10 -20	USA (Colorado)	11
Beta Blockers			
Atenolol	<RL - 506	USA (Skaneateles Lake, New York)	15
Lipid Regulators			
Gemfibrozil	<RL - 620	USA (La Pine Oregon, Florida, Colorado, Minnesota), Canada (Ontario)	1, 5, 6
Bezafibrate	Nd - 12	Canada (Ontario)	1
Antiepileptics			
Carbamazepine	<RL - 450	USA (La Pine, Oregon, Montana, Colorado, Skaneateles Lake, New York	
Anticoagulants			
Warfarin	<RL - 23000	USA (La Pine, Oregon, Montana)	5, 3, 4

Table 2.4 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Steroid Hormones			
Estrone (E1)	Nd - 260	USA (Cape Cod-Massachusetts, North Carolina, Skaneateles Lake, New York)	2 , 13, 15
17β-estradiol (E2)	Nd - 84	USA (Cape Cod-Massachusetts, North Carolina, Skaneateles Lake, New York)	2, 13, 15
17α-ethynyl estradiol	Nd - 36	USA (North Carolina, Skaneateles Lake, New York)	13, 15
Estriol (E3)	<RL - 380	USA (North Carolina)	13
Coprostanol	<RL-7100000	USA (La Pine, Oregon, Colorado)	5, 7
Cholesterol	<RL- 2200000	USA (La Pine, Oregon, Colorado)	5, 7
H2 Blockers & Antihistamines			
Cimetidine	Nd - 12000	USA (La Pine, Oregon, Montana, Colorado)	5, 3, 7
Ranitidine	<RL - 10^5	USA (La Pine, Oregon, Montana)	5, 3
Diphenhydramine	72	USA (La Pine ,Oregon)	5
Antiasthmatic		USA (La Pine, Oregon, Montana)	
Salbutamol	<RL	USA (La Pine, Oregon)	5
Antihypertensives			
Diltiazem	<RL	USA (La Pine, Oregon)	5
Anthelmintic			
Thiabendazole	<RL	USA (La Pine, Oregon)	5
Personal Care Products			
Insect repellent			
DEET	<RL - 52000	USA (La Pine, Oregon, North Carolina)	5, 10
Sunscreen Agents			
Homosalate	4490	USA (North Carolina)	10
Oxybenzone	<RL - 151	USA (Skaneateles Lake, New York)	15
Antimicrobial			
Triclosan	Nd - 82000	Canada (Ontario), USA (Golden-Colorado, Colorado, Woodville-Florida, Skaneateles Lake, New York)	1, 6, 7, 11, 12, 14, 15
Triclocarban	<RL - 270	USA (Skaneateles Lake, New York)	15

Table 2.4 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Life style compounds			
Stimulants			
Caffeine	<RL - 9300000	USA (Cape Cod, La Pine, Oregon, Montana, Colorado, Golden ,Colorado, New England, Woodville-Florida, Greenville, North Carolina,	2, 5, 6, 3, 4, 7, 9, 11, 12, 14, 15, 10
1,7-dimethylxanthine	10^5 – 1010000	USA (Cape Cod, La Pine, Oregon, Montana, Colorado, Woodville-Florida, Greenville)	2, 5, 3, 4, 7, 14
Nicotine	10^5	USA -Montana	3
Cotinine	10^5 - 3900	USA (Cape Cod, La Pine, Oregon, Montana, Colorado)	5, 3, 7
Food additives			
Indole (Fragrance)	<RL - 220000	USA (La Pine, Oregon)	5
Methyl salicylate (Fragrance)	1600	USA-Colorado	7
Menthol (Flavoring)	<RL - 160000	USA (Cape Cod, La Pine, Woodville-Florida, Greenville)	5, 14
Triethyl citrate	<RL - 11000	USA (La Pine, Oregon)	5
Industrial Compounds			
Surfactants			
DAS	1670 - 2040	USA (Cape Cod)	2
DSBP	2.8 – 6.5	USA (Cape Cod)	2
EDTA	3800 - 1700000	USA (Cape Cod, Colorado)	2, 6, 7, 11, 12
NTA	1300 - 130000	USA (Colorado)	7, 12
Surfactant metabolites			
4-nonylphenol	<RL - 650000	USA (Cape Cod, La Pine, Oregon, Colorado, Golden ,Colorado North Carolina)	2, 4, 6, 8,
NP1EC	7800 - 91000	USA (Cape Cod, Massachusetts, Colorado)	2, 11, 12
NP2EC	1600 - 2300	USA (Cape Cod, Massachusetts)	2
∑NPEO	3900 - 170000	USA (Cape Cod, Massachusetts, Colorado)	2, 7
∑NPEC	50000 - 320000	USA (Colorado)	7
∑OPEO	<RL - 160000	USA (Colorado)	7
4-n-Octylphenol	570 - 3000	USA (Colorado)	7
4-t-Octylphenol	1600 - 220000	USA (Colorado)	7
4-Propylphenol	2600 - 4000	USA (Colorado)	7
4-t-Pentylphenol	<RL - 660	USA (Colorado)	7
4-Ethylphenol	7500 - 15000	USA (Colorado)	7

Table 2.4 (Continued)

Compound	Concentration ng^{-1}	Country / Sampling Location	References
4-Methylphenol	4500000	USA (Colorado)	7
2,6 di-t-butylphenol (2,6-DTBP)	<RL	USA (Colorado)	7
Flame retardants and plasticizers			
Flame retardants			
TCEP	<RL - 1900	USA (La Pine Oregon)	5
TPP	<RL - 900	USA (La Pine Oregon)	5
Plasticizers			
TBEP	20000	USA (New England)	9
Bisphenol A	<RL - 14900	USA (Cape Cod, Skaneateles Lake, New York, Florida, Colorado, Minnesota	8, 15, 6
Disinfectants			
Phenol	10000	USA (Woodville, Florida)	14
P-cresol		USA (La Pine Oregon, Woodville, Florida)	5, 14
Phenylphenol	1000	USA (Cape Cod)	8
Perfluorinated Compounds			
PFOA	5.7 – 38.8	USA (Skaneateles Lake, New York)	15
PFOS	Nd – 94.4	USA (Skaneateles Lake, New York)	15
PFBS	Nd – 4.0 ng/L	USA (Skaneateles Lake, New York)	15
PFHpA	Nd – 12.9	USA (Skaneateles Lake, New York)	15
PFHxA	3.67 – 99.0	USA (Skaneateles Lake, New York)	15
PFHxA	Nd – 2.48	USA (Skaneateles Lake, New York)	15
PFOSA	Nd – 6.56	USA (Skaneateles Lake, New York)	15
PFNA	0.83 – 4.95	USA (Skaneateles Lake, New York)	15
PFUnDA	Nd-0.92	USA (Skaneateles Lake, New York)	15
PFDoDA	Nd-5.91	USA (Skaneateles Lake, New York)	15

Table 2.4 (Continued)

Compound	Concentration ng^{-1}	Country /Sampling Location	References
Fumigants			
1,2-dichlorobenzene	<RL	USA-Colorado	7
1,3-dichlorobenzene	<RL	USA-Colorado	7
Deodorizer			
1,4-dichlorobenzene	2100 - 59000	USA-Colorado	7
Other compounds			
Anthraquinone (Bird repellent)	1100	USA-Colorado	7
1,4-benzoquinone (Benzene metabolite)	2600 - 3100	USA-Colorado	

1 - Carrara et al., (2008) **2** - Swartz et al., (2006) **3** - Godfrey et al., (2007) **4** - Godfrey & Woessner, (2004) **5** - Hinkle et al., (2005) **6** - Conn et al., (2010) **7** - Conn et al., (2006) **8** - Rudel et al., (1998) **9** - Phillips et al., (2015) **10** - Del Rosario et al., (2014) **11** - Conn & Siegrist, (2009) **12** - Conn et al., (2010) **13** - Stanford & Weinberg, (2010) **14** - Katz et al., (2010) **15** - Subedi et al., (2014); **DAS** (2-disulfonate); **DSBP** (4,4-bis(2sulfostryl)biphenyl); **DTBP** (2,6 di-t-butylphenol); **∑NPEO** (NP1EO - NP3EO); **∑NPEC** (NP1EC - NP3EC); **DEET** (N,N-diethyl-meta-toluamide); **PFBS** (Perfluoro butane sulfonate; **PFOS** (Perfluoro octane sulfonate); **PFOSA** (Perfluoro octane sulfonate); **PFHxA** (Perfluoro hexanoic acid); **PFHPA** (Perfluoro heptanoic acid; **PFOA** (Perfluoro octanoic acid); **PFNA** (Perfluoro nonanoic acid); **PFDA** (Perfluoro decanoic acid; **PFUnDA** (Perfluoro undecanoic acid); **PFDoDA** (Perfluoro dodecanoic acid); **NTA** (Nitro acetic acid); **EDTA** (Ethylenediamine acetic acid); **∑NPEC** (Sum of 4-nonylphenol mono-ethoxy carboxylate through 4-nonylphenol tetra-ethoxy carboxylate); **∑NPEO** (Sum of 4-nonylphenol mono-ethoxylate through 4-nonylphenol tetra-ethoxylate); **∑OPEO** (Sum of 4-tert-octylphenolmonoethoxylate through 4-tert-octylphenoltetraethoxylate); **TBEP** (tris (2-butoxyethyl) phosphate; **TPP** (Triphenyl phosphate); **TCEP** (tris(2-chloroethyl) phosphate; **NP1EC** (4-Nonylphenolmonoethoxycarboxylate); **NP2EC** (4-Nonylphenoldiethoxycarboxylate); **NPEO** (Nonylphenol Ethoxylates); **NPEC** (Nonylphenol Ethoxy carboxylate); Nd (not detected); **<RL** (less than reporting level)

2.4.1.3 Antibiotics

Antibiotics are a therapeutic class with wide application in human therapy and veterinary medicine for the purpose of preventing or treating microbial infections (Boxall et al., 2003; Kümmerer, 2009). Antibiotics belonging to various classes (e.g. sulfonamides, macrolides, tetracyclines and fluoroquinolones) have been detected in onsite wastewater and downgradient groundwater in the United States and Canada. In several studies, the two most frequently detected antibiotics in STE and groundwater were trimethoprim and the sulfonamide, sulfamethoxazole (Hinkle et al., 2005; Godfrey et al., 2007; Godfrey & Woessner, 2004; Katz et al., 2010; Subedi et al., 2014; Conn et al., 2006; Conn & Siegrist, 2009; Schaider et al., 2014; Schaider et al., 2016; Verstraeten et al., 2005; Phillips et al., 2015; Dougherty et al., 2010). In STE, trimethoprim and sulfamethoxazole levels were reported at the range of 70 to 10^5 ng/L and 40 to 37700 ng/L respectively. In comparison, the magnitude of the concentrations of trimethoprim and sulfamethoxazole in groundwater was lower and ranged from 0.7 to 580 ng/L and 40 to 1330ng/L respectively. Reduced concentrations of these compounds in groundwater across studies may likely indicate that trimethoprim and sulfamethoxazole are well attenuated during vadose zone (referring to the unsaturated zone that extends from the surface to groundwater table and provides contaminant breakdown through aerobic oxidation) transport. Other antibiotics have been reported less frequently (<4 studies) in STE and include the fluoroquinolones (ciprofloxacin, norfloxacin and ofloxacin), the broad spectrum antibiotic tetracycline (tetracycline), and the macrolides (azithromycin, erythromycin and erythromycin-H2O (dehydrated metabolite of erythromycin). In Colorado, Conn et al. (2006) reported the occurrence of tetracycline in a multifamily septic tank at levels up to 20000 ng/L. Erythromycin in onsite wastewater was reported in three case studies conducted in the United States (Godfrey et al., 2007; Conn et al., 2006; Conn & Siegrist, 2009); erythromycin levels were as high as 18000 ng/L in a high school septic tank in Montana (Godfrey et al., 2007). With the exception of compounds such as sulfamethoxazole, trimethoprim, ciprofloxacin and erythromycin-H2O which have co-occurred in onsite wastewater and

groundwater, other antibiotics, including two fluoroquinolones, enrofloxacin and sarafloxacin have been found in groundwater downgradient from septic systems even though their occurrence in STE has not been reported elsewhere (Verstraeten et al., 2005). In Cape Cod, three sulfonamides, sulfamethiozole, sulfathiazole and sulfachloropyridazine were dected at trace concentrations (0.2 to 1.0 ng/L) each only one time in drinking water supply wells finished in unconfined sand and gravel aquifer, in an area with widespread use of septic systems (Schaider et al., 2014, 2016).

2.4.1.4 Lipid Regulators

Lipid regulators as well as their metabolites have been found in STE and groundwater from the United States and Canada (Carrara et al., 2008; Hinkle et al,. 2005; Conn et al., 2010). Gemfibrozil, the most frequently reported antilipemic, was found to occur in groundwater in four case studies with maximum concentration up to 1950 ng/L detected in groundwater samples from Ontario, Canada (Carrara et al., 2008). Gemfibrozil however, was reported less frequently in onsite wastewater (n = 3), with concentrations ranging from near the reporting levels (0.1 ng/L) in single family septic tanks investigated in Florida, Colorado and Minnesota (Conn et al., 2010) to 620 ng/L in onsite wastewater from Ontario Canada (Carrara et al., 2008). In La Pine Oregon, gemfibrozil concentration in septic tank effluent was close to 10 ng/L, similar to measured concentrations in groundwater samples in the same study (Hinkle et al., 2005). Other lipid regulators have also been reported to occur in groundwater. Schaider et al. (2016) tested public water supply wells in Cape Cod for organic wastewater contaminants and reported for the first time, the occurrence of simvastatin, (a commonly used cholesterol lowering agent) in drinking water samples at levels up to 14 ng/L. Clofibric acid and bezafibrate were reported to occur in Canadian groundwater at concentrations of 15 and 350 ng/L respectively (Carrara et al., 2008) ; clofibric acid however, was not detected in samples of onsite wastewater in the same study. Fenofibrate was among the target compounds investigated but not detected in a high school

septic tank in Montana (Godfrey et al., 2007) and in onsite wastewater and groundwater in Ontario (Carrara et al., 2008).

2.4.1.5 Antiepileptics

Carbamazepine, a widely used antiepileptic, was the most commonly reported compound in this subgroup, and has been reported in STE (n = 5) and groundwater (n=4) in several studies across the United States (Conn et al., 2006; Hinkle et al., 2005; Godfrey et al., 2007; Godfrey & Woessner 2004; Subedi et al., 2014; Schaider et al., 2014; 2016). Highest maximum carbamazepine concentrations were similar in both onsite wastewater (450 ng/L) and groundwater (210 ng/L); suggesting the persistent nature of carbamazepine (Conn et al., 2006). Two antiepileptic drugs, phenytoin and primidone were not reported in STE, but they have been reported to occur in groundwater in New York at concentrations up to 100 ng/L (Phillips et al., 2015) and up to 66 ng/L in drinking water supply wells in Cape Cod (Schaider et al., 2016; 2014).

2.4.1.6 Hormones and Sterols

This group of compounds consists of sex hormones, plant estrogens, fecal indicators and plant sterols, some of which have been identified as endocrine disrupting substances (EDS) (Standley et al., 2008). Natural estrogens and contraceptives including estrone (E1), 17β-estradiol (E2), estriol (E3), estrone 3-sulphate (E1-3S) and 17α-ethinyl estradiol (EE2) were found to occur in STE and groundwater across the United States (Swartz et al., 2006; Stanford & Weinberg, 2010; Subedi et al., 2014; Phillips et al., 2015). The main source of steroid estrogens in wastewater is excretion, where they may be present in urine as biologically inactive conjugates and in faces as biologically active free steroids (Gomes et al., 2005). Concentrations of E1 and E2 in onsite wastewater, each reported in three case studies, ranged from 11.3 to 260 ng/L and 19 to 84 ng/L, respectively (Swartz et al., 2006; Godfrey et al., 2007; Subedi et al., 2014). In a study to determine the migratory potential of organic wastewater contaminants in the subsurface, Swartz

et al., (2006) noted that the magnitude of the concentrations of E1 (120 ng/L) and E2 (45 ng/L) in onsite wastewater was similar to that observed groundwater; a similarity the authors attributed to the effect of continuous discharge of effluent to the subsurface with poor removal of the estrogens during migration through the vadose zone. Likewise, Phillips et al. (2015) found the concentrations of E3 (2.5 ng/L), the main excretion product of natural estrogens in humans (Ternes et al., 1999) and E1 (4.2 ng/L) in groundwater recharged by septic systems comparable to concentrations in effluent discharges from activated sludge wastewater treatment. E3 and EE2 (a synthetic steroid estrogen with wide application in many formulations of combined oral contraceptive pills) have been detected in STE in North Carolina and New York (Stanford & Weinberg, 2010; Subedi et al., 2014). In Cape Cod, concentrations of estrone 3-sulphate, the main urinary excretion product of estrone (Ternes et al., 1999) in groundwater was in the range 1.0 to 4.0 ng/L (Swartz et al., 2006). The persistence of E1-3S in groundwater has been linked to its chemical structure, which according to Gomes et al. (2005) consists of a sulphate moiety which is not easily cleaved. Schaider et al. (2016) reported the occurrence of two steroid hormones, progesterone (0.02 ng/L) and cis-testosterone (0.04 ng/L) in domestic water wells in Cape Cod. Two sterols, cholesterol and its metabolite coprostanol have also been reported to occur, though less frequently ($n < 3$) in onsite wastewater and groundwater (Table A.A1 and Table A.A2). The maximum concentrations of cholesterol and coprostanol in onsite wastewater from Summit and Jefferson Counties in Colorado were 2.2×10^6 ng/L and 7.1×10^6 ng/L, respectively (Conn et al., 2006); however, lower maximum concentrations (3500 ng/L and 10^4 ng/L, respectively) were reported to occur in groundwater form Golden, Colorado (Conn & Siegrist, 2009).

2.4.1.7 Other Pharmaceuticals

Other classes of pharmaceuticals used as antacids, antihistamines, anti-asthmatics, anti-hypertensives, anticoagulants, antifungals, antidepressants, anxiolytics, anthelmintic and antianginal drugs have been found to occur in onsite wastewater and in groundwater affected by

these systems in the United States. Warfarin, an anticoagulant, was reported to occur in onsite wastewater in three case studies at concentrations below the reporting level (10 ng/L) to up to 2.3 x 10^4 ng/L (Hinkle et al., 2005; Godfrey et al., 2007; Godfrey & Woessner, 2004) (Table 2.4), but was found to occur at much lower concentrations (10 ng/L) (Table 3) in groundwater (Hinkle et al., 2005; Verstraeten et al., 2005). Two antacids, cimetidine and ranitidine were found in both onsite wastewater and groundwater in La Pine Oregon (Hinkle et al., 2005); the occurrence of ranitidine in onsite wastewater at concentrations as high as 10^5 ng/L was also reported in Montana but cimetidine was not detected (Godfrey et al., 2007); cimetidine levels in non-residential septic systems in Colorado reached 1.2 x 10^4ng/L, with a median concentration of 280 ng/L (Conn et al., 2006). Hinkle et al. (2005) found that the concentration of the antihistamine, diphenhydramine was up to 70 times higher in STE (72 ng/L) as compared to groundwater samples (1.0 ng/L). Salbutamol (anti-asthmatic) was detected in both onsite wastewater and groundwater samples from La Pine Oregon at concentrations near 200 ng/L (Hinkle et al., 2005) but was tested for and not detected in single family and high school septic tanks in Montana (Godfrey et al., 2007; Godfrey & Woessner, 2004). Nifedipine (antianginal) and diltiazem (antihypertensive) were not detected in onsite wastewater from Montana (Godfrey et al. 2007) but diltiazem and the metabolite of nifedipine, dehydronifedipine were reported to occur in both onsite wastewater and groundwater samples from La Pine Oregon (Hinkle et al., 2005). In Nebraska, dehydronifedipine was also detected in a shallow sand point well at a low concentration (3 ng/L) (Verstraeten et al., 2005). Fluoxetine (antidepressant) and metformin (antidiabetic) were investigated but not detected in a high school septic tank in Montana (Godfrey et al. 2007). Other pharmaceutical compounds including two muscle relaxants, butalbital and carisoprodol; a sedative, phenobarbital, a topical anesthetic, lidocaine and an antianxiety agent, meprobamate have been found to occur at concentrations exceeding 100 ng/L in groundwater (Table 2.3) in New England, United States (Phillips et al., 2015). In Cape Cod, lower maximum concentrations were reported for meprobamate in public (5.4 ng/L) and domestic (2 ng/L) drinking water supply wells located

in areas served by septic systems (Schaider et al., 2014; 2016). Thiabendazole (anthelmintic) was reported in onsite waste water and groundwater samples from La Pine Oregon at levels below 10 ng/L (Hinkle et al., 2005). In New England, fluconazole (antifungal) was detected once in groundwater samples at concentrations below 100 ng/L (Phillips et al., 2015).

2.4.2 Life Style Compounds

Caffeine was found in more than four case studies reporting its occurrence in onsite wastewater (n = 10) and groundwater (n = 6) in the United States; likewise, its metabolite, 1,7-dimethylxanthine was found to occur frequently in onsite wastewater (n = 6) and groundwater (n = 4). The maximum concentrations for caffeine and 1,7-dimethylxanthine in STE were in the range 10^4 to 9.3 x 10^6 ng/L and 10^4 to 1.01x10^6 ng/L respectively. The highest maximum caffeine concentration (9.3x 10^6 ng/L) was detected in non-residential septic tanks serving convenience stores in Colorado (Conn et al., 2006); the authors attributed such elevated caffeine levels to both human excretion, high consumption and the subsequent disposal of unconsumed caffeinated beverages. In groundwater samples, highest maximum concentrations for caffeine and 1,7-dimethyxanthine were nearly the same (1710 and 1730ng/L respectively), and by contrast three orders of magnitude lower than concentrations observed in samples of onsite wastewater (10^6 ng/L). Although nicotine and its metabolite cotinine were less frequently reported in onsite wastewater and groundwater, maximum cotinine concentrations in onsite wastewater were in the range 9.2 x 10^2 to 10^5 ng/L (Hinkle et al., 2005; Godfrey et al., 2007; Conn et al., 2006), but the magnitude of cotinine concentrations in groundwater samples was lower (1.0 to 60 ng/L) in the three case studies reporting its occurrence in groundwater (Godfrey et al., 2007; Verstraeten et al., 2005; Schaider et al., 2016). Nicotine was reported only in a single study but at concentrations as high as 10^5 ng/L in onsite wastewater and ranged from near 25 to 50 ng/L in groundwater samples from Montana (Godfrey et al., 2007).

2.4.3 Personal Care Products

Personal care product (PCP) ingredients, including antimicrobials, sunscreen agents, insect repellents and synthetic musk fragrances have been detected in onsite wastewater and groundwater samples across the United States and Canada. Triclosan (an antimicrobial) was the most frequently reported compound in onsite wastewater (n = 7), with concentrations in the thousands of ng/L range (Conn et al., 2006; Conn & Siegrist, 2009; Conn et al., 2010; Carrara et al., 2008; Katz et al., 2010; Subedi et al., 2014 Conn et al., 2010a]. Triclosan average maximum concentration was 3.5 x 10^4 ng/L, with highest detection of 8.2 x 10^4 ng/L in a non-residential septic tank in Colorado (Conn et al., 2006). Conn et al., 2010 found triclosan residues in all raw wastewater and septic tank effluent samples from six single family households investigated in three states in the United States. The ubiquitous occurrence of triclosan in onsite wastewater across the literature may reflect the regular use of triclosan-containing personal care products (such as toothpastes, hand soaps, mouth washes, cosmetics, deodorants, body sprays, lotions and skin cleansers) which eventually become part of the domestic waste stream; by comparison, triclosan concentrations in groundwater samples were much lower than measured levels in STE and were in the range 7 ng/L to 500 ng/L (Carrara et al., 2008; Conn & Siegrist, 2009). The relatively lower concentrations in groundwater samples confirm the claim that triclosan is easily removed in confined treatment units (Conn et al., 2006), and this may explain why elevated levels of triclosan in groundwater are unlikely. Other PCPs such as oxybenzone, a sunscreen agent and triclocarban, an antimicrobial agent have also been detected in onsite wastewater at 151 ng/L and 270 ng/L respectively (Subedi et al., 2014). Another sunscreen agent homosalate was detected in a residential septic tank in North Carolina at a mean concentration of 4.4 x 10^3 ng/L (Del Rosario et al., 2014). In groundwater samples from the United States, DEET, an active ingredient in insect repellents was the most frequently reported PCP (n=6); maximum concentrations ranged from below detection limit (2.5) to 800 ng/L (Table 2.3) (Hinkle et al., 2005; Dougherty et al., 2010). Two synthetic musk fragrances, galaxolide and tonalide, which are

known endocrine disrupting substances (EDS) (Caliman & Gavrilescu, 2009) were reported to occur in groundwater samples from New York, Florida and Oregon, at a range below levels of detection to levels above 100 ng/L (Hinkle et al., 2005; Phillips et al., 2015; Katz et al., 2010). Although the sunscreen agent benzophenone has not been reported to occur in onsite wastewater, it was detected in groundwater samples from New York at concentrations exceeding 100 ng/L (Phillips et al., 2015).

2.4.4 Food Additives

Food additives detected in samples of onsite wastewater and groundwater across the United States include a series of chemical compounds used as stabilizers, flavorings, fragrances and sweeteners. Triethyl citrate, added in food as a foam stabilizer and also with uses in pharmaceutical coating and plastics (Stuart et al., 2011), was found in STE from La Pine, Oregon at concentrations as high as 11000 ng/L (Hinkle et al., 2005) but at relatively lower concentrations (> 100 ng/L) in groundwater samples from New York (Phillips et al., 2015). In the La Pine, Oregon study, other food additives were found to occur in onsite wastewater samples at concentrations up to 220000 ng/L for indole (a fragrance in coffee) and 160000 ng/L for menthol (a flavoring in cigarettes, cough syrups and mouth wash). Katz et al. (2010) also reported high concentrations (>10000 ng/L) of menthol in onsite wastewater samples from Woodville Florida. Methyl salicylate (a fragrance in food and liniment) was detected in samples of onsite wastewater from Colorado at concentrations reaching 1600 ng/L (Godfrey et al., 2007). In domestic drinking water wells in Cape Cod, acesulfame (an artificial sweetener) was extensively distributed, being detected at a maximum concentration up to 5300 ng/L in 85% of samples that also contained measurable levels of other chemicals (Schaider et al., 2016); according to the authors, the dominance and co-occurrence of acesulfame with other chemicals in groundwater samples suggest that acesulfame is likely, an ideal marker of wastewater impact. Two synthetic phenolic substances, 2,6-di-tert-butyl-4-methylphenol (BHT) and 3-tert-butyl-4-methoxyphenol (BHA), commonly used in finished

foods and cosmetic formulations to slow down oxidative processes (Lanigan & Yamarik, 2002) were identified below reporting levels (0.5 µg/L) in groundwater samples from Colorado (Conn & Siegrist, 2009).

2.4.5 Industrial Compounds

Several industrial compounds including surfactants and their metabolites, disinfectants, flame retardants, plasticizers and solvents have been reported in studies investigating their presence in onsite wastewater and groundwater across the United States.

2.4.5.1 Surfactants and Surfactant Metabolites

Alkylphenol ethoxylates (APEO) are a group of non-ionic surfactants with a wide range of domestic and industrial applications, particularly in cleaning product formulations and other consumer products such as paints, cosmetics and pesticides (Ying et al., 2002). The predominant forms of APEOs reported across the literature, as expected, were the primary degradation products of APEOs, alkylphenols (APs), nonylphenol (NP) and octylphenol (OP) as well as their ethoxylates (NPE1-4, OPE1-4). APEO metabolites have been identified as hormonally active substances known to persist during wastewater treatment (Ying et al., 2002; Lapworth et al., 2012; (Conn et al., 2010). 4-Nonylphenol, a primary breakdown product of nonylphenol ethoxylate (NPEO) (Mao et al., 2012), was the dominant surfactant metabolite in onsite wastewater (n=8) and groundwater (n=4). Highest NP concentrations were reported in single family septic tanks (6.5×10^5 ng/L) in Florida, Colorado and Minnesota (Conn et al., 2010) and in groundwater samples (8.4×10^4 ng/L) collected from a shallow sandy aquifer in Cape Cod, Massachusetts (Swartz et al. 2006). Other nonylphenol-derived compounds (bio-transformed from the parent NPEO surfactants) have also been reported. Nonylphenol mono-ethoxylate (NP1EO) and nonylphenol mono-ethoxy carboxylate (NP1EC) were detected in onsite wastewater and were each reported in three case studies, at maximum concentration in the range of 3.4×10^3 to10^6 ng/L for NP1EO and 8.2×10^3 to 9.1×10^4 ng/L for NP1EC (Conn et al., 2010; Conn & Siegrist

2009; Conn et al., 2010a; Swartz et al., 2006). High NP1EO concentration (10^6 ng/L) reported in effluents from single family septic tank was associated with the biodegradation of NPE containing dish and laundry detergents (Conn et al., 2010). In Cape Cod, NPIEC was detected in samples from monitoring wells collected at varying exploratory depths, at concentrations below level of detection to 3.5 x 10^4 ng/L (Swartz et al., 2006), whereas in drinking water wells NP1EC was not detected above reporting levels of 0.26 µg/L (Rudel et al.,1998). In groundwater samples downgradient of an infiltration bed, Swartz et al. (2006) found NP2EC concentration (6.9 x 10^4 ng/L) to be at least one order of magnitude higher than levels in onsite wastewater (2300 ng/L); the authors linked higher levels in groundwater samples to the likelihood that NP2EC was produced faster than it was attenuated during subsurface transport. The sum concentration of nonylphenol mono to triethoxylates (∑NPEO = NP1EO+NP2EO+NP3EO) in onsite wastewater from Cape Cod was in the range 3900 to 4800 ng/L (Swartz et al., 2006). Likewise, in Colorado, Conn et al. (2006) reported the occurrence of ∑NPEO (combined sum of NP1EO through NP4EO (4-nonylphenoltetraethoxylate) in both residential and non-residential septic tanks at maximum concentrations of 8.3 x 10^4 ng/L and 1.7 x 10^5 ng/L respectively; elevated concentration of ∑NPEO in nonresidential septic tanks (e.g. convenience stores and food establishments) again, was attributed to the typical use of cleaning products in commercial establishments. Although 4-tert-octylphenol and 4-tert-octylphenolmonoethoxylate through 4-tert-octylphenoltetraethoxylate (∑OPEO=OP1EO+OP2EO+OP3EO+OP4EO) were less widely reported across the reviewed literature, they occurred in all veterinary hospital effluent samples from Colorado, at concentrations as high as 1.6 x 10^5 ng/L and 2.2 x 10^5 ng/L respectively (Conn et al., 2006). In two separate Colorado studies, the detection of the non-ionic surfactant metabolites, 4-n-octylphenol, 4-t-octylphenol, 4-propylphenol, 4-ethylphenol and 4-methylphenol in groundwater samples at relatively lower concentrations (<RL to 530 ng/L) (Conn & Siegrist, 2009) compared to onsite wastewater levels (3000 to 4.5x10^6 ng/L) (Conn et al.2006), may indicate that these compounds were well attenuated during onsite wastewater treatment.

In addition, other detergent components also have been detected in onsite wastewater and groundwater samples from the United States. Carrara et al. (2008) found two fluorescent whitening agents, diaminostilbene (DAS) and distyrylbiphenyl (DSBP) in onsite wastewater, at maximum concentrations of 2040 ng/L and 6.5 ng/L respectively. In the same study, measured concentrations of DAS (4180 ng/L) and DSBP (27 ng/L) in groundwater samples were comparable to levels in onsite wastewater. The similarity in magnitude of concentrations, as previously noted for NP1EC, highlights the likely persistence of these contaminants in groundwater due to the effect of continuous recharge of groundwater by septic effluent, with minimal time for effluent renovation during subsurface transport. EDTA, a metal chelating agent, used in hand and bar soaps, lotions and also as a builder in laundry detergents was frequently detected in effluents from septic tanks (n = 5) and was reported in the range 10^4 to 10^5 ng/L (Conn et al., 2006; Swartz et al., 2006; Conn & Siegrist, 2009; Conn et al., 2010; Conn et al., 2010a). In Colorado, EDTA was frequently detected in STE from residential (all 30 samples) and non-residential (all 32 samples) sources; the highest concentration of EDTA occurred in non-residential septic systems at 1.7×10^6 ng/L (Conn et al., 2006). Nitrilotriacetic acid (NTA), another metal chelating agent, was only studied in Colorado and was reported in two case studies. Unlike EDTA, highest level of NTA (1.3×10^5 ng/L) was detected in residential septic tanks (Conn et al., 2006). In groundwater samples, EDTA was detected less frequently (n=2), but maximum concentrations from two case studies were both high, 1.9×10^4 ng/L (Swartz et al., 2006) and 4.4×10^4 ng/L (Conn & Siegrist, 2009) and within the same order of magnitude, confirming the claim that EDTA is not easily removed by sorption and biodegradation during soil treatment (Conn & Siegrist, 2009) and consequently are likely to persist in groundwater. Unlike EDTA, NTA, was found in groundwater samples at less than the reporting levels (0.5 µg/L), likely due to its relatively more biodegradable characteristic (Conn & Siegrist, 2009).

2.4.5.2 Perfluorinated Compounds

Perfluoroalkyl substances (PFASs) are a variety of compounds with wide spread use in industrial applications and consumer products including carpeting, textile coatings, polishes, fire retarding foams, upholstery, non-stick cook ware, paper packaging, cosmetics, electronic and photographic devices (Giesy & Kannan, 2002). The extensive use and release of PFASs, together with their unique chemical and thermal stability, have resulted in their abundance in various environmental matrices (Buck et al., 2011). A variety of PFASs have been detected in both septic tank effluent and groundwater samples from the United States. In a pilot study to determine the effectiveness of advanced onsite treatment systems to protect receiving environments, Subedi et al. (2014) found eleven PFASs in effluents from septic systems serving multiple households along Skaneateles Lake in Central New York. PFASs detected were reported at a median concentration range of 0.20 to 14 ng/L and included PFBS (perfluorobutane sulfonate), PFDS (perfluorodecane sulfonate), PFDA (perfluorodecanoic acid), PFDoDA, (perfluorododecanoic acid), PFHpA (perfluoroheptanoic acid), PFHxA (perfluorohexane sulfonate), PFHxA (perfluorohexanoic acid), PFNA (perfluorononanoic acid), PFOSA, (perfluorooctane sulfonamide), PFOS (perfluorooctane sulfonate) PFOA (perfluorooctanoic acid) and (PFUnDA (perfluoroundecanoic acid). Five of these compounds have also been reported in drinking water supply wells elsewhere; PFOA and PFOS were found in public drinking water wells in Cape Cod with maximum concentrations of 22 ng/L and 97 ng/L, respectively (Schaider et al., 2014). PFOA and PFOS represent the earliest detections of PFASs in human samples, which provoked subsequent investigations into the fate and toxicological effects of PFASs (Giesy & Kannan, 2002). A similar study was also conducted in the same area, where domestic water supply wells were screened for the presence of PFASs and other wastewater organic contaminants. In this study, Schaider et al. (2016) detected four groups of PFASs including PFOS, PFBS, PFHpA and PFHxS at a concentration range of 1 to 41 ng/L in samples of domestic drinking water supply wells.

2.4.5.3 Flame Retardants and Plasticizers

Organophosphorus flame retardants (OFRs) and plasticizers, which have broad uses in many consumer products including plastics, textiles, antifoam, dyes, floor polish and electronics have been identified in onsite wastewater and groundwater samples from the United States. Four compounds detected in both onsite wastewater and groundwater samples include TCEP (tris(2-carboxyethyl)phosphine, TPP (triphenyl phosphate), TBEP (tris (2-butoxyethyl) phosphate) and bisphenol A. Concentrations of TCEP, the most frequently detected flame retardant in samples of groundwater ranged from <RL (0.04 ng/L) to > 100 ng/L. (Dougherty et al., 2010; Hinkle et al., 2005; Phillips et al., 2015; Schaider et al., 2014). Low concentrations of TCEP (20 ng/L) were found in three of 20 public supply wells in Cape Cod (Schaider et al., 2014), similar to the average concentration found in a shallow groundwater affected by onsite wastewater discharges in Liberty Bay, Massachusetts (Dougherty et al. 2010). In New York, TCEP concentration was greater than 100 ng/L in shoreline wells downgradient of several septic systems serving a densely populated area (Phillips et al., 2015). Although reported less frequently in onsite wastewater (n=1), TCEP level in septic tank effluent from La Pine, Oregon was as high as 1900 ng/L but was well attenuated in groundwater with concentrations below the reporting level of 0.04 ng/L (Hinkle et al., 2005). In the same study, TPP was also observed in onsite wastewater at 900 ng/L, but was found at a lower concentration in drinking water wells (14 ng/L) in Cape Cod (Schaider et al., 2016). In New England, Phillips et al. (2015) observed high and comparable concentrations ($2x10^4$ ng/L) of TBEP in effluents from septic holding tanks and groundwater samples. In this study, the dominance of TBEP (contributing over 85%) with respect to other plasticizers (TCEP) was associated with extensive use of cleaning products at an extended health care facility. Bisphenol A, a plasticizer and fungicide, was present in onsite wastewater and reported in three case studies at a maximum concentration range of 150 to 1.49 $x10^4$ ng/L (Subedi et al., 2014; Conn et al., 2010; Rudel et al., 1998]. In Cape Cod, bisphenol A was detected in drinking water wells at 4 ng/L (Schaider et al., 2016) and 44 ng/L (Rudel et al., 1998). Relatively more OFRs have been

found to occur in groundwater as compared to onsite wastewater. This was evidenced by the exclusive detections of TDCPP, TCPP, TEP, TBP and 2-EHDP in samples of groundwater. TDCPP (tris dichloropropyl phosphate) concentrations in groundwater ranged from below limit of detection (0.1 µg/L) to about 100 ng/L (Hinkle et al., 2005; Katz et al., 2010; Schaider et al., 2014). In Cape Cod, four OFRs TCPP (tris (chloroisopropyl) phosphate), 2-EHDP (2-ethylhexyl diphenyl phosphate), TEP (triethyl phosphate) and TBP (tributyl phosphate) were detected in domestic and public drinking water supply wells impacted by onsite wastewater, at maximum concentrations of 40 ng/L, 15 ng/L, 38 ng/L and 11 ng/L respectively (Schaider et al., 2014; 2016). TBP concentration was less than 100 ng/L in La Pine aquifer (Hinkle et al., 2005).

2.4.5.4 Other Industrial Compounds

Other classes of industrial compounds such as disinfectants, solvents, fumigants and preservatives have been found to occur in onsite wastewater and down gradient groundwater in the United States. In Woodville Florida, two disinfecting agents, phenol and p-cresol, (the latter also identified as a wood preservative), were detected in onsite wastewater samples at concentrations as high as 10^4 ng/L (Katz et al., 2010). In the same study, phenol in groundwater samples from a Karst aquifer (i.e. fractured rock aquifers) was an order of magnitude lower (10^3 ng/L). P-cresol was also detected at elevated concentrations (1.3×10^6 ng/L) in STE samples from La Pine, Oregon (Hinkle et al., 2005), whereas a relatively lower concentration (2900 ng/L) was detected in groundwater samples from Minnesota (Erickson et al., 2014). In Colorado, 1,4-dichlorobenzene (a deodorizer) and 1,4-benzoquinone (benzene metabolite), respectively varied between (2100 ng/L and 5.9×10^4 ng/L) and (2600 ng/L and 3100 ng/L) in onsite wastewater from residential and non-residential septic tanks (Conn et al. 2006). In the same study, two fumigants 1,2-dichlorobenzene and 1,3-dichlorobenzene were detected below reporting levels (0.5 µg/L). By comparison, with the exception of 1,4-benzoquinone detected at relatively much lower concentrations (<5µg/L), 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,4-dichlorobenzene in

groundwater samples reported elsewhere were similar <RL (0.5µg/L) (Conn & Siegrist, 2009). In La Pine, Oregon, tetrachloroethane (PCE) levels in samples of groundwater were <100 ng/L. The review of occurrence of EOCs in onsite wastewater and downgradient groundwater has shown that EOCs belonging to various chemical classes can be found in onsite wastewater and downgradient groundwater. Individual compounds were detected at various concentrations in STE and groundwater and the levels and frequency of occurrence have been attributed to several factors including type and quantity of product consumed, water use and conservation practices (Conn & Siegrist, 2009) and physicochemical properties of EOCs which determine their fate during wastewater treatment (e.g. septic systems) and in the environment during subsurface transport. In the following section, the fate and behavior of EOCs in septic systems and in underlying groundwater are discussed.

2.5 Fate of EOCs in Septic Systems and Subsurface Environment

The environmental fate of any chemical compound is governed by numerous factors and processes (Boxall et al., 2004), primarily the physical and chemical properties including partition coefficients, solubilities or kinetic constants, which characterize different dynamic processes such as biotic and non-biotic mediated reactions (e.g. biodegradation, hydrolysis, photodegradation, sorption and volatilization) (Guillén et al., 2012). Although little is known about the fate of EOCs in septic systems (Conn et al., 2006), their removal during onsite wastewater treatment is known to be specific to each compound and differs considerably across locations (Toor et al., 2014; Conn & Siegrist, 2009). It is therefore, difficult to generalize EOC behavior during onsite wastewater treatment, given the peculiarity of individual compounds and sites (Conn et al., 2006). For example, while over 90% of caffeine is removed in septic tanks (Matamoros et al., 2008), surfactants are known to be poorly removed (Conn et al., 2006).

In addition to the influence of physico-chemical properties on EOC removal, research has shown that EOC behavior in the septic tank and soil absorption unit is controlled by various metabolic and natural attenuation processes, which may enhance EOC removal from wastewater and effluent (Schaider et al., 2013). The three main pathways for EOC removal during onsite wastewater treatment include 1) biotransformation, which is the conversion of parent compounds to metabolites or degradates with equal or greater environmental relevance depending on their persistence or toxicological disposition (Boxall et al., 2004; Lapworth et al., 2012); 2) sorption, referring to the adsorption of chemical contaminants to solid surfaces such as soil particulate matter and bio-solids (Margot et al., 2015) ; and 3) volatilization, the conversion of soluble EOCs to volatile gases released into the atmosphere (Toor et al., 2014). Removal of EOCs in wastewater can occur through one or a combination of these mechanisms and may differ considerably, depending on several factors including the physicochemical characteristics of the compounds, such as hydrophobicity, volatility, biodegradability and polarity (Conn & Siegrist, 2009; Toor et al., 2014), the nature of the environmental receptor (Sui et al., 2015; Farré et al., 2008), environmental related factors including geochemical settings (Lapworth et al., 2012) and the type of confined treatment unit (Conn et al., 2006). Besides the physicochemical properties, operational conditions of the treatment unit, such as the hydraulic loading rate, can also influence the removal of EOCs. The loading rate of EOCs into the soil infiltration area and the type of treatment unit will determine the ease and extent of contaminant removal during treatment (Conn et al., 2006). According to Conn & Siegrist (2009), compounds such as caffeine, triclosan and I, 4-dichlorobenzene, which easily sorb to solids remain trapped with the settled septic tank solids (septic sludge), whereas, recalcitrant contaminants or their metabolites, (e.g. EDTA, NPEC), which are poorly removed from raw wastewater may be loaded into the infiltration area at nearly the same concentration as that in the raw sewage (Godfrey et al., 2007).

2.5.1 Biotransformation

Biodegradation, which may occur within the septic tank or in the soil absorption area can determine the fate of EOCs during onsite wastewater treatment (Toor et al., 2014). As mentioned before, the physicochemical characteristics of a compound including its structure, solubility, partition coefficient, ionization constants and stability are known to play a vital role in the behavior of EOCs, including the rate of degradation during wastewater treatment and subsurface migration (Schaider et al., 2013). For example, the presence of sulfur in sulfamethoxazole, chlorine in diclofenac and the double benzene ring in ketoprofen (Kimura et al., 2005) appear to be the structural properties responsible for their resistance to biodegradation and consequently, their persistence during wastewater treatment (Heberer 2002b). Studies have shown that substances which do not sorb easily to solids (such as nitrilotriacetic acid, (NTA)) may be bio-transformed under aerobic or anaerobic conditions (Conn & Siegrist, 2009). Attenuation of some EOCs in septic tanks via the biodegradation mechanism relies on the microbial activity of the prevalent anaerobic population (Del Rosario et al., 2014), however, owing to limited microbial diversity and low oxygenation conditions in septic tanks, biodegradation activity is reduced, which often results in the low removal (<50%) and persistence of EOCs in septic tank effluents (Swartz et al., 2006; Godfrey et al., 2007; Conn et al., 2009); septic tanks therefore, serve mainly as settling units for solids and consequently, the chemical quality of raw wastewater (influent) is oftentimes, comparable to the liquid leaving the septic tank (effluent) into the soil environment (Conn et al., 2006). It need to be said that biodegradation does not necessarily mean absolute removal of contaminants, since parent compounds may be transformed to metabolites with more persistent or toxicological tendencies (Boxall et al., 2004; Toor et al., 2014). For instance, the biotransformation of the nonionic surfactant (NPE) during wastewater treatment results in the formation of complex degradation products, which are known hormonally active substances including 4-nonylphenol, NPEO and NPEC (Lapworth et al., 2012). Although researchers have recognized the importance of characterizing the transformation products of parent compounds

during wastewater treatment (Toor et al., 2014); Morasch 2013), this knowledge gap is yet to be well addressed in studies assessing removal efficiencies of contaminants during wastewater treatment (Toor et al., 2014). Thus, considering that minimal treatment of wastewater occurs in septic tanks, the absolute treatment of wastewater depends therefore on the effectiveness of the soil absorption unit and the underlying soil area to adequately remove wastewater contaminants through various physical, chemical and biological processes; a treatment potential which is hoped to bring about the percolation of a more clarified effluent through the subsurface prior to groundwater recharge (Carroll et al., 2004; Schaider et al. 2013; Del Rosario et al. 2014).

2.5.2 Sorption

Sorption can be an effective mechanism for EOC removal during onsite wastewater treatment (Conn & Siegrist, 2009). The propensity for hydrophobic contaminants, (including nonvolatile OWCs) with large octanol/water partition coefficient (K_{ow}) to sorb to bio-solids or septic sludge (Toor et al., 2014), or to organic carbon in soil treatment units (Teerlink et al., 2012) results in the eventual loss of sorbed contaminants through filtration or sedimentation (Conn et al 2006). For example, triclosan and 4-nonylphenol with $\log K_{ow}$ of 4.35 and 4.70 respectively, were eliminated by sorption in both tank-based and wetland based systems (Conn et al., 2006). Controlled laboratory scale experiments conducted by Conn & Siegrist (2009) to evaluate the role of sorption in the removal of a surrogate pharmaceutical during soil treatment indicated that sorption to soil was crucial to the loss of Rhodamine WT(RDT) during migration through the vadose zone. They suggested that contaminants whose chemical structures are similar to RDT may likely be removed by sorption during soil treatment. Thus, it is obviously that the main constituents of wastewater effluent released to the soil absorption area would be degradation products (e.g. NPEC compounds) or the more water soluble untransformed compounds (e.g. EDTA), which would often occur at similar concentrations to raw wastewater (Conn et al., 2006). The partitioning of pollutants between solid and aqueous phases is therefore significant in demonstrating the fate

and migration potential of substances in the subsurface and also the degree to which chemicals can be taken up by organisms (bioavailability) (Ruffino & Zanetti, 2009). The sorption potential for EOCs rely upon three primary factors: i) the fundamental properties of the chemical being adsorbed (sorbate) including molecular size, solubility and functional groups; ii) liquid phase characteristics including pH, temperature and ionic strength and iii) sorbent characteristics of the substance that adsorbs the chemical (sorbent) including surface area, organic matter content, mineral surfaces and pore size (Ruffino & Zanetti, 2009). It important to mention that in certain cases, the attenuation of a substance can occur by both sorption and biodegradation processes. For example, nonvolatile compounds appear to be susceptible to removal by sorption and biotransformation during confined unit treatment, particularly for compounds with large octanol/water partition coefficient (Conn & Siegrist, 2009). While sorption of OWCs to solids with subsequent removal by sedimentation or filtration are effective removal mechanisms in septic tank based systems, for compounds with large $K_{ow,}$ such as triclosan (log K_{ow} = 4.35) (Lindström et al., 2002), triclosan removal can also occur via biotransformation depending on the type of treatment unit. For example, additional triclosan removal was observed in filter-based systems and this was attributed to aerobic biotransformation and subsequent filtration of particulates containing sorbed triclosan (Lindström et al., 2002). Hence, more soluble compounds (hydrophilic) which tend to withstand removal by sorption, can for the most part, be removed by biodegradation.

2.5.3 Volatilization

Volatilization can be a substantive elimination pathway during onsite wastewater treatment, particularly for volatile organic compounds (VOCs) (Conn et al., 2006); however, the type of treatment unit can influence the potential for removal of EOCs through volatilization. VOCs with large Henry's law constant (K_H), can easily be removed using onsite treatment units which provide conducive environment such as air-stripping, as the case with bio-filter based systems (Conn et

al., 2006; Matamoros et al., 2016). Therefore, treatment units with minimal air-water exchange, as the case with tank-based systems may not effectively eliminate VOCs DeWalle (1980) cited in (Conn et al., 2006). Furthermore, other conditions such as low hydraulic retention time (HRT) in tank-based systems contribute significantly to the ineffective removal of nonvolatile organic compounds in septic tanks (Conn & Siegrist, 2009); the authors found that compounds are often poorly removed in septic tanks because the estimated tank-based volatilization half-lives for nonvolatile organic compounds (e.g. triclosan >1 Year), are often times much longer than HRTs, and are subsequently released to the environment.

There have been questions concerning the fate of EOCs that are not easily affected by sorption or biodegradation during wastewater treatment. EOCs which remain un-sorbed to solids (e.g. particulate matter) or which resist microbial breakdown during onsite treatment have been poorly removed, resulting in their persistence either in the septic tank or soil absorption area or underlying groundwater (Schaider et al., 2013). The low removal (7-12%) of EDTA in all treatment systems studied by Conn and coworkers (2006) was attributed to the reduced sorption and biotransformation potential of EDTA during wastewater treatment.

Several studies have investigated the fate of EOCs in the subsurface as well as their migratory potential, which ultimately determines their occurrence in the underlying groundwater (Swartz et al., 2006; Swartz et al., 2006; Godfrey et al., 2007;Toor et al., 2014). Fate of EOCs in the subsurface can vary substantially (Conn & Siegrist, 2009), and subsurface transport of EOCs may or may not lead to significant attenuation of EOCs prior to groundwater recharge. In Montana, Godfrey et al. (2007) found reduced concentrations (BDL) of most pharmaceutical compounds in the underlying groundwater following migration through 2m sand-dominated vadose zone. The apparent removal of these compounds was attributed to one or more processes including sorption to the vadose zone (or aquifer media) or the microbial conversion of parent compounds into degradates. Conversely, compounds such as sulfamethoxazole and carbamazepine, which are

poorly attenuated during vadose zone transport can be persistent and have been detected at measurable concentrations in shallow groundwater (Verstraeten et al., 2005; Phillips et al., 2015; Hinkle et al., 2005) and drinking water supply wells (Schaider et al., 2014; Schaider et al., 2016). This preferential removal underscores the immense significance of compound specific removal during wastewater treatment (Toor et al., 2014), and also, highlights the influence of geochemical settings and aquifer conditions on EOC removal (Godfrey et al., 2007).

2.6 Conclusion

This review highlights the vulnerability of groundwater to septic system discharges. Widespread contamination of groundwater resources by a cocktail of EOCs has been observed at environmentally relevant concentrations (referring to concentrations greater than 100 ng/L). Notable EOCs include a range of pharmaceutical compounds, PCPs, industrial compounds, lifestyle compounds and food additives. Ibuprofen, carbamazepine, sulfamethoxazole, trimethoprim, triclosan, caffeine and its metabolite 1,7, dimethyl xanthine and 4-nonylphenol were the most widely reported compounds in onsite wastewater and groundwater in Canada and across the United States. Another group of investigators studying groundwater contamination from various sources reported similar findings regarding pharmaceutical pollution of groundwater (Lapworth et al., 2012). The occurrence of EOCs in groundwater used as a drinking water source potentially threatens human heath following long term exposure through drinking water intake. Regulating septic system use and establishing monitoring protocols are needed in areas where septic systems are predominantly used to treat sewage and where groundwater is a primary source of drinking water.

Chapter 3

Survey of use and disposal of pharmaceuticals and personal care products and willingness to pay for groundwater protection program in Nigeria

3.1 Introduction

The use of pharmaceuticals and personal care products (PPCPs) has become an unavoidable part of daily life. Pharmaceutical use is increasing in both hospitals and households, and these compounds, which currently include over 1500 active pharmaceutical ingredients (APIs) (Boxall et al., 2012), are produced in large volumes yearly, for use in therapy, disease prevention, and diagnosis (Boxall et al., 2012; Fent et al., 2006; Bound and Voulvoulis, 2005; Daughton and Ruhoy, 2008). In the European Union, many of these chemicals are currently used in medicines as analgesics, antibiotics, oral contraceptives, beta-blockers, tranquilizers, and impotence drugs, amongst others (Ternes et al., 2004).

Furthermore, with the growing effort to improve access to medicines through local production (United Nations, 2011), pharmaceutical use has also increased substantively in many low and middle income economies (Access to Medicine Foundation, 2018). In Nigeria for example, the rapidly growing pharmaceutical industry has improved access to and common use of both prescription and over-the-counter (OTC) medicines across the population (Federal Ministry of Health, 2010), and recent projections suggest that this trend will continue in the coming years, with the Nigerian pharmaceutical industry expected to generate up to US$11 billion in pharmaceutical sales by 2020 (Manufacturing Pharma, 2015).

Likewise, in the quest to improve the quality of daily life, there has been extensive use of a variety of household products, including an array of personal care products (PCPs) (e.g. cosmetics,

fragrances, shampoo, body lotions, moisturizers, sunscreen agents, deodorants, lipsticks, hair dyes, skin whiteners, toothpaste, mouth wash), household cleaning agents (e.g. detergents, disinfectants), anti-oxidants, stabilizers, household pesticides, additives, and preservatives (Boxall et al., 2012; Villa et al., 2012 ; Ternes et al., 2004).

The usefulness of most consumer products has been attributed largely to the active chemicals they contain, which confer on them, specific properties, functionality and quality. (Egeghy et al., 2012; Kephalopoulos et al., 2007). Although the expansion of the chemical industry has generally been agreed to have brought immense benefits to modern society, particularly in regards to global economic growth, improved health, longevity and standard of living (Wilson & Schwarzman, 2009), concerns have been raised regarding the potential for many of the chemical constituents of PPCPs to cause harm to the natural environment. Many of the chemical constituents of PPCPs, which are continuously released as parent compounds or their metabolites (Monteiro & Boxall, 2010), have been detected in various environmental media (aus der Beek et al., 2016), and their impact on the environment and potential risk to humans have not been fully understood (Christian G. Daughton & Ruhoy, 2009).

In this regard, the issue of chemical emissions in the environment, particularly PPCPs, has in recent times attracted considerable attention. Boxall and colleagues in an influential debate, raised critical questions regarding the release of PPCP residues to the environment and the possible human health and ecological impact (Boxall et al., 2012). It was then generally agreed that there is an urgent need for a better understanding of the sources of PPCPs, their mode of entry to the environment, dominant exposure pathways in different regions, as well as the ramifications for human health following unintended human exposure through various routes.

Considering the mode of PPCP entry into the environment, several sources and pathways have been identified, and among these, individual human activity such as usage and disposal of a wide

range of consumer products and wastewater treatment have been recognized as significant sources and route of entry of PPCPs into the environment (Daughton and Ruhoy, 2009; Ruhoy and Daughton, 2007; Ruhoy and Daughton, 2008; Glassmeyer et al., 2009; Schaider et al., 2016; Bound and Voulvoulis, 2005). The contributions of API usage to the environmental presence of pharmaceutical residues can be attributed to the partial utilization of medicines by the body following therapeutic use, whereby unused fractions often enter the wastewater system when excreted in urine and faeces, as a combination of intact and metabolized pharmaceuticals (Jjemba, 2006). Also, residues remaining on the skin after dermal application of pharmaceuticals can be released by bathing or excreted in sweat (Daughton and Ternes, 1999; Daughton and Ruhoy, 2009; Kotchen et al., 2009; Richardson et al., 2005). Similarly, PCP active ingredients enter wastewater systems during showering or bathing (Richardson et al., 2005), and a majority of other household products (e.g. cleaning agents), are characteristically 'down-the-drain' products, because they end up in sewer systems after use (Keller, 2006).

The disposal of accumulated pharmaceuticals (e.g. expired, unwanted or unused medications), has recently been identified as a significant contributor to the overall presence of pharmaceuticals in the environment, as accumulated products not used in housholds must eventually be discarded (Daughton and Ruhoy, 2009). Consequently, several studies have investigated the disposal pattern of unused medications and why medicines accummulate in households. Their findings highlight a wide range of causative factors including - expiry, patient non-adherence, over-prescribing, or excessive purchase (Daughton and Ruhoy, 2009); reuse or to give to someone who had similar symptoms (Auta et al., 2011); bereavement and change of medications (Ekedahl, 2006); improved or resolved medical conditions (Braund et al., 2009); unclear instructions, inconvenience in dosing schedule, forgetfulness and a poor perception of the severity of the illness (Coma et al., 2008; Vellinga et al., 2014; Ruhoy and Daughton, 2007).

Leftover medicines can be discarded by an end-user through various disposal options, including discarding in garbage bins, disposing to sewerage (i.e. flushing down the toilet / sink) or where available, through medicine takeback programs (Daughton and Ternes, 1999; Garcia et al., 2013; Glassmeyer et al., 2009). Overall, stockpiling medications and eventual disposal of leftovers can have huge economic, health and environmental consequences (Kümmerer, 2008). From the health and economic perspectives, Ruhoy and Daughton (2007), identified accidental poisoning of humans and pets and possible drug diversion as important public health and safety concerns, in addition to the huge financial losses incurred due to medication wastage. From the environmental perspective, medicine disposal practices of consumers through the garbage bin is environmentally unfavorable, given that, engineered landfills or solid waste dumps, which are the ultimate receptors of household wastes, may pose significant threats to unprotected groundwater, through the leaching of landfill effluent (Slack et al., 2005; Braund et al., 2009). Discarding to sewerage by flushing leftover medications in toilets and sinks can increase the environmental load of pharmaceutical residues (Daughton, 2003) and other down the drain products. Frequent detections of OWCs in water systems (e.g. surface water, groundwater and finished drinking water), have been associated with the poor removal rate of OWCs in wastewater treatment systems (Carrara et al., 2008; Swartz et al., 2006; Del Rosario et al., 2014), which in general, are not primarily designed to remove such contaminants, particularly those that occur in trace levels in the waste stream (Ternes et al., 2004; Phillips et al., 2015).

The occurrence of a wide range of PPCPs, including analgesics, antimicrobials, anticonvulsants, triclosan, surfactant metabolites, stimulants, phthalates, endocrine disrupting compounds and household pesticides in water supplies (Carrara et al., 2008; Del Rosario et al., 2014; Conn and Siegrist, 2009; Phillips et al., 2015; Katz et al., 2010,; Kolpin et al., 2002; Schaider et al., 2016), has led to concerns about exposure to PPCPs through drinking water intake and subsequent assessments of potential human health risks (Schwab et al., 2005; Cunningham et al., 2009;

Houtman et al., 2014); nonetheless, the extent of human effects of exposure to PPCPs remains largely unknown.

With uncertainties surrounding the potential human health effects of PPCP exposure, there have been, in recent times, heightened efforts by government authorities and organizations in many advanced countries to curtail the quantity of PPCPs entering the environment (Ruhoy and Daughton, 2008; Kotchen et al., 2009). Most of the steps taken have been country-wide initiatives, which promote and implement adequate disposal methods such as medicine take-back programs, to allow consumers to return unwanted or expired medications for safe disposal (Glassmeyer et al., 2009). By comparison, such programs are yet to be initiated in many low-income countries, and it is not clear whether the public in such countries, would be willing to participate in or pay a fee for such programs.

Furthermore, research on use and disposal patterns of consumer products, particularly pharmaceuticals, has also been focused on high income countries (Kookana et al., 2014). This means that usage and disposal information, which may highlight the types and quantities of chemical emissions reaching the local environment (Teng et al., 2012), and which may be imperative to establishing realistic exposure estimates (Price et al., 2010; Biesterbos et al., 2013), and monitoring protocols (Kookana et al., 2014.; Franco et al., 2016], for risk assessment is hardly available in low to middle income countries. In Nigeria, for example, drug use information regarding the class and quantities of pharmaceuticals consumed is limited, even though the demand and widespread use of both prescription and over-the-counter medicines across the population has increased over the last two decades owing to improved access to medicines (Federal Ministry of Health, 2010).

Interestingly, Kostich et al. (2010) outlined various ways by which pharmaceuticals consumed in a country can be estimated, including the use of marketing data, wastewater data, survey of API

dispensations and the use of manufactured and imported data as an inventory of total available volume of APIs. Among these approaches, the use of surveys to estimate API use seemed to be the most practicable option for Nigeria, given that API sales and prescription data are not readily available, and the wastewater data approach to estimate consumption is not feasible, as it requires monitoring API levels in sewerage systems where there is sewer connectivity (Kookana et al., 2014). This study therefore, aimed to 1) quantitatively estimate PPCP consumption through survey of use in Nigerian households; 2) identify current disposal practices for leftover APIs and PCPs; and 3) assess participants' pro-environmental attitude and willingness to pay for groundwater protection program. Assessing pro-environmental attitude was vital as it has proved to be a strong predictor of pro-environmental behaviors, such as the willingness to pay for an environmental good (Kaiser et al., 1999; Stern et al., 1995).

3.2 Methods

3.2.1 Study Design

A cross-sectional questionnaire-based study was conducted in southern Nigeria between March and June 2016 using a mixed mode approach for data collection. The self-completion questionnaire was administered online and via household drop-off. We envisaged that an online survey, though quicker and cheaper, may lack the needed coverage, particularly in rural areas with limited access to the internet. Hence, questionnaires were distributed to households in two geopolitical zones in southern Nigeria (south-south and south-east), with a combined population of approximately 31,999,230 inhabitants (Nigeria Data Portal, 2016). These zones were chosen based on accessibility, convenience and the potential to be representative of many Nigerian urban and rural settings.

3.2.2 Pilot Study

The pilot study was performed in February 2016 to determine the feasibility of the study protocol, test the measurement instrument (a questionnaire) and to evaluate the survey approach. The questionnaire was pre-tested on 30 households, with the intent to determine whether the questionnaire items correctly address the research needs and that the questions were well-defined, understandable and appropriate. The consent form was also pretested for understanding. The questionnaire was divided into four sections relating to socio-demographic characteristics of respondents, PPCP usage and disposal pattern, pro-environmental attitude and behaviour and willingness to pay (WTP) for groundwater protection programs. The questionnaire required self-completion by participants with the help of research assistants. Three main issues were observed among participants in the pilot of the questionnaire and included: 1) understanding of the questionnaire items and the terminology used; 2) Length of the questionnaire (the time spent to complete the questionnaire) and 3) format (in terms of layout and font size). The results from the pilot study showed that participants did not respond to some of the questions in the API usage section either because the items were imprecise, or the terminology used was incomprehensible to many participants. This was observed with items which used the chemical name of the drug rather than the advertised brand name and with the items asking how much API is consumed in the household rather than how much the participant consumed; this resulted in ambiguity, with the participants not being able to estimate API use for every member of the household. These problems were solved by using the advertised brand names rather than the generic names of individual APIs and questions concerning API usage were rephrased to address individual rather than household API consumption. Only PCP usage was estimated on a household level given that most of the items may be used collectively in the households. Regarding the time spent to complete the questionnaire, research assistants explained the study to participants in about 3 – 5 minutes, and on average, participants took 60 minutes or more to complete the questionnaires. Completing the questionnaire in 60 minutes or more rather than the anticipated completion time

of 30 minutes was likely due to the length of the questionnaire, which was observed with several items at the last sections of the questionnaire not being completed by some participants and the request for more time to complete the questionnaire. To solve this problem, questionnaires were dropped off and collected the following day. Although this was added expense to the study given the extra transportation cost required to retrieve completed questionnaires, it afforded the participants more time to complete the questionnaire to improve the response rate. In addition, the questionnaire was closely spaced with small font size to reduce the number of printed copies to save cost; this resulted in small prints that were difficult to read and likely contributed to the increased time required to complete the questionnaire. This issue was resolved by reformatting the questionnaire. The pretested questionnaire was improved by considering all the flaws discussed and then administered to households.

3.2.3 Full Survey

Following the pilot studies, questionnaires were administered online using the 'Qualtrics' online survey software (www.qualtrics.com), while paper copies were distributed to households. Because of the absence of a national sampling frame (e.g. population register), distribution of questionnaires involved a multi-step stratified sampling strategy, whereby the study sample units (i.e. households) were recruited by stratifying local government areas (selected randomly from the zonal map), into different political wards. Within each ward, households were selected as potential sampling units without prior identification, through a systematic random sampling technique, which involved data collectors skipping between appropriate numbers of households in each political ward. Only residential buildings were included in the random sample selection process, and for multi-residential units (e.g. block of flats), households within these units were also randomly selected. In the event of a nonresponse, rejection and inaccessibility, the next building or household unit was then selected. Research assistants were given a two-day training to provide background information about the study and data gathering technique using

questionnaires. Ethical clearance was obtained from the University of York Environment Department Ethics Committee before the commencement of the study.

Four hundred households were surveyed with the pretested questionnaire, comprising a series of questions in multiple choice, open ended and Likert scale formats, structured along four sections. In the first three sections, information was gathered about sociodemographic and housing characteristics, usage and disposal practices of pharmaceuticals and personal care products, and pro-environmental attitudes and behaviour. The fourth and concluding section, consisted of a contingent valuation (CV) type question, designed to determine the value of a proposed groundwater protection program, measured through participants' willingness to pay (WTP) using a payment scale approach. The context to inform participants' decision to protect groundwater resources from PPCP contamination is detailed in the questionnaire in the Appendix (Table A.B1). The expectation was that the information provided in the survey will result in an estimation of mean WTP amount for the proposed groundwater protection program. Study objectives, benefits, risks, confidentiality of responses and the right to voluntary participation were explained to participants. Inclusion in the study required that at least the household informant was present and voluntarily agreed to participate in the study (with no incentives for participation) by signing a written informed consent. The household informant is anyone who contributes to household income and is knowledgeable about household expenditure. We excluded any household informant who did not agree to a written informed consent. In addition to the above survey group, a few local pharmacies, drug stores, convenience stores and markets were visited to obtain information on the most commonly demanded medicines and personal care product brands to be selected for evaluation. A total of 293 of the 400 paper questionnaires were retrieved, the response rate being 73%. Only 57 participants completed the online survey. In total, 350 participants were included in further analysis.

3.2.4 Estimating API Usage

Estimates of API consumption was determined with two structured questions: 'Which is the most commonly used medicine?' and 'How often do you use this medicine or any other not included in the list?' The latter question had the same response options for each medicine and spanned through seven frequency of use levels, ranging from 'never' to 'daily use'. To estimate API use, frequency of use codes of 0, 4, 12, 36, 52, 156 and 365 respectively, were assigned to the following frequency of use levels: 'Never', Once/3months, 'Once/month', '2-3times/month', 'Once/week', '2-3 times/week', and 'Daily'. Participants who 'Do not Remember' frequency of API use were assigned monthly use values. Annual API use in grams per capita per year was calculated using Equation 3.1

$$\boldsymbol{Average\ API\ use\ (grams\ per\ capita\ per\ year)} = \frac{\boldsymbol{DOT * DDD}}{\boldsymbol{Number\ of\ Participants}} \qquad \textbf{(3.1)}$$

Where: DOT is the days of therapy (i.e. number of days for which a person was treated in a year) and refers to a calculated field obtained by multiplying the frequency of use codes by the number of API users – (for example, based on the assigned frequency of use codes, DOT for 62 participants who have reported using an API once a month is 744); DDD is the defined daily dose which is a unit of measurement expressing 'the assumed average maintenance dose per day for a drug used for its main indication in adults' (WHOCC, 2018).

3.2.5 Estimating PCP Usage

Estimates of PCP use was determined with two structured questions: 'Which of the following brand of product is most commonly used in your household?' and 'What quantity of product is consumed in your household weekly?' Amount of product consumed was presented as retail quantities in volume (e.g. 50mL, 100mL, 250mL, 500mL, 750mL, 1000mL) or masses (e.g. 10g,

50g, 100g, 200g, 250g, 500g, 750g, 1000g) of the different product brands listed in the questionnaire (Table A.B1). Calculations assumed that 1 mL is equivalent to 1 gram and were based on a slightly modified algorithm from a similar study (Rotsidou and Scrimshaw, 2015). The calculation in Equation 3.2 averaged use amongst participants to give an estimate of average annual use of PCP per household.

$$Average\ PCP\ use\ (\frac{\frac{Litres}{Household}}{Year} = \frac{Quantity\ used * Frequency\ of\ use * Number\ of\ Households}{Number\ of\ participants * 1000} \quad (3.2)$$

Where: PCP is personal care product; 1000 is the conversion factor (i.e. milliliter to liters).

Using product labels, we also identified the type and percentage composition of the primary active ingredient in each product brand. Estimates of active ingredients were calculated based on the estimated average annual PCP use per household.

3.2.6 Measurement of Environmental Attitudes and Behaviour

Measurement of environmental attitudes was based on items which relate to multiple attitudinal components, including verbal commitment (which measures what a person states they are willing to do); actual commitment (which measures what a person actually does), and affective component (which measures the degree of emotionality towards environmental issues) (Maloney et al., 1975). Measurement of verbal commitment was based on two commitment statements (e.g. 'I would be willing to recycle more if convenient recycling facilities were available'; I would be willing to properly dispose of solid wastes if convenient places were available) and participants were asked to indicate on a 5-point scale, the extent they agree with each statement; measurement of actual commitment was based on a 6-item scale selected from a previous study (Wesley and Zelezny, 1998), that requested an indication of how often, on a 5-point scale (ranging from 'never' to 'all of the time'), they had engaged in each of six specific behaviours (e.g. buying

eco-friendly products; recycling bottles/cans/plastics) in the last year; measurement of the degree of emotionality towards environmental issues was based on a 3- item scale (e.g. 'It makes me happy when government policies protect the environment'; 'I am happy when I do things that protect the environment'; 'I worry about environmental problems'), that requested an indication of the extent, on a (5-point scale) they agreed with each statement. It is assumed that a higher score in the attitudinal scale would imply higher pro-environmental attitudes and behaviors.

3.2.7 Measurement of WTP for groundwater protection program

WTP was determined in three ways using carefully worded statements. First, respondents were asked about their willingness to participate in a proposed groundwater protection program, which comprises 1) a medicine takeback program that will allow end users to return leftover medications to collection centres (e.g. local pharmacies), and 2) a government intervention scheme for wastewater management, to ensure that septic systems are properly designed and adequately maintained to optimize treatment efficiency and protect groundwater. For this, respondents had two response options: 'Yes' or 'No'. Second, respondents were given the option to make a monthly contribution to a groundwater protection fee, by indicating from a list of possible sums in a payment card format, the range that best describes their WTP monthly-fixed contribution to support the proposed groundwater protection program and to consider this payment as an added taxation that would reduce their budget for other goods. The following range of monthly WTP amount associated with the intervention was proposed: 500-2000 naira ($2 - $8), 2250-3750 naira ($9 - $15) and 4000-5500 naira ($16 - $22), and respondents who answered 'no' to the first question (i.e. protest zero or negative WTP), were asked to give reasons for stating a zero bid. Given that there are no pre-existing pollution reduction measures in the study area, WTP could not be presented to respondents as 'improved' services for pre-existing conditions but as 'stated preferences'. This approach, according to previous research, allows participants to be asked what they would do under hypothetical but realistic circumstances (Rowlands et al., 2003). Our

main goals were to determine households' willingness to participate in groundwater protection program, the amount they would be willing to pay, and the factors which may affect both participation and the amount households would be willing to pay.

3.2.8 Data analyses and statistics

The data were analysed with the SPSS 24.0 (IBM SPSS Statistics) statistical software. We tested for statistically significant association between pro-environmental attitudes and willingness to participate in groundwater protection program, and for sociodemographic and economic correlates of WTP amount using regression analysis. The willingness to participate regression model contained four explanatory variables including 1) concern for risk of groundwater contamination; 2) perceived personal responsibility to protect the environment; 3) Need of government policies to protect the environment and 4) Need of modern waste management facilities. The WTP regression model examined association of age, gender, household income and level of education completed across the range of payment offer values. The results are presented as odds ratios (OR), and with a 95% confidence interval (CI), a p-value of less than 5% was considered statistically significant.

3.3 Results and Discussion

3.3.1 Demographic, socioeconomic and housing characteristics of households

The sample of 350 participants did not show any gender bias, with 48% (male) Versus 52% (female); the age of participants was in the range 20 to 60 years, with an average age of 37 years (SD±10.6). Forty-three percent (n=151) were married with children and one-third (n=118) of participants hold a university degree or its equivalent (Table A.B2). Although 60% (n=210) of participants rated their financial situation to be good or very good, nearly half (45%) of households had a combined monthly income of 50,000 naira (US$ 200) or less in the year preceding the

survey; this amounts to US $6.60 a day which is above the international poverty line of US $1.90 a day (United Nations, n.d.). However, it needs to be said that recent report by the United Nations Development Program (UNDP) indicates that at least 62% of the Nigerian population lives in extreme poverty, which is the inability to meet the most basic needs such as health, education, access to water and sanitation (UNDP, 2016).

Seventy-one percent (n=247) of participants reported urban residence but it is likely that there may be an over-representation of urban habitation. According to Bloch et al. (2015), Nigeria, in recent times, is experiencing progressive merging of many small and medium villages and towns into nearby urban areas; a scenario resulting in substantive rural to urban reclassification. Information about housing type shows variation in the quality of housing and type of facilities. Concerning sewage treatment, 315 participants (90%) treat sewage using septic systems. Only one in four households (n=88) are connected to mains water supply; most households (67%; n=235) meet their water needs by tapping groundwater resources using boreholes (39%) and shallow hand dug wells (28%) and more than three-quarter (78%; n = 273) of participants do not treat source water before use. It is interesting to note that most of our results complement earlier findings from a national demographic household survey (National Population Commission, 2014).

3.3.2 API Usage

A high proportion (93.1%, n = 326) of participants rated their health to be ‘good’ or ‘very good’ and 228 participants (65%) had used about three to five different APIs in the four weeks preceding the survey. Average quantities of APIs used per capita per year ranged from 0.037 g (triprolidine, a nasal decongestant) to 92.7 g (paracetamol, an analgesic) (Table 3.1.) The relatively high consumption of paracetamol is in line with reports documenting extensive global use of analgesics over the last two decades (Hamunen et al., 2008); this has been associated with the use of analgesics as first-line medicines in the symptomatic treatment of pain and fever (Blondell et al.,

2013). There have also been countrywide investigations into patterns of analgesic use in many countries, and reports from these investigations show widespread use of paracetamol and other analgesics. For example, a study investigating national consumption of opioid and nonopioid analgesics in Croatia found paracetamol to be the most highly consumed medication in its group for the year under analysis (Krnic et al., 2015). Other analgesics, such as ibuprofen have also been used substantively in many countries, including Australia, China, Malaysia, Canada, the United Kingdom (Krnic et al., 2015) and Lebanon (Massoud et al., 2016); by comparison, our study found ibuprofen to be the least reported analgesic by participants.

For the treatment of malaria, participants reported more frequent use of artemether and lumefantrine (DOT = 3872), compared to chloroquine (DOT = 308) and quinine (DOT = 772). The relatively higher reported use of artemether/lumefantrine is not surprising, given the recent switch from the use of monotherapy to artemisinin-based combination therapies (ACT) for malaria treatment. In 2006, an updated WHO guideline for the treatment of malaria recommended ACT as the first-line drug for the treatment of uncomplicated malaria in endemic regions, following the resistance of Plasmodium falciparum to other antimalarial drugs (World Health Organization, 2015b); subsequently, many countries including Nigeria, have progressively updated their treatment policy from the use of monotherapy with such drugs as chloroquine to the currently recommended ACT (UNIDO, 2011; World Health Organization, 2015b).

Participants reported the use of a broad range of antibiotics, and the six most commonly used antibiotics include ampicillin, tetracycline, ciprofloxacin, cloxacillin, sulfamethoxazole and trimethoprim; estimated average annual per capita use of antibiotics varied and ranged from 0.66 g (trimethoprim) to 18.0 g (ampicillin). Because we have not measured adequacy of consumption, which requires the use of adequacy of consumption measure to analyse needs (Krnic et al., 2015), it is not possible to determine whether the consumed amounts correspond with the needs of patients and cannot conclude if these medicines are misused. Nonetheless, antibiotic self-

medication, promoted by over the counter accessibility of antibiotics in many developing countries, is one of the leading contributors of antimicrobial resistance, therapeutic failures and adverse health outcomes (Versporten et al., 2014; Goossens et al., 2005), and unless action is taken to regulate the use of anti-infective medicines, the WHO warns about serious consequences for individual and public health (WHO, 2003).

Self-medication and uncontrolled dispensing, particularly with antibiotics have been identified as a public health concern requiring immediate action in many countries such as Serbia (Tomas et al., 2017), and several other east European countries (Versporten et al., 2014a). Because developing countries have been recognized to have disproportionately heavy disease burdens and inadequate measures to control the spread of infections (World Health Organization, 2014), a call for action against the non-prescription use of antibiotics in Nigeria is imperative, particularly as its rapidly growing population continues to face a hugely underdeveloped health care system.

Interestingly, the range of medicines consumed by participants are in the list of essential medicines (World Health Organization, 2015a), and about 45% (n = 158) of participants reported that they often obtained medications without prescription. Given the potential for abuse of medicines, particularly non-prescription medicines (Bissell et al., 2001; Cooper 2013), there is need to set quantitative targets for rational drug use through a national action plan (Versporten et al., 2014b), and to promote rational use by raising knowledge and awareness levels of physicians, pharmacists, allied health personnel and the public, as currently practiced in Turkey (Turkish Medicines and Medical Devices Agency, 2017). Our findings are therefore, intended for policy makers and healthcare professionals to increase awareness of medicine dispensing and consumption behaviour and the impetus to improve medicine use patterns across communities, through the development and enforcement of rational use policies.

Participants also reported the frequent use of three antifungals, including miconazole, terbinafine and clotrimazole; however, actual quantities consumed could not be estimated owing to lack of DDD values. Assigning DDDs to topical use preparations such as these has been reported as a challenge, as daily doses vary considerably among individuals due to differences in intensity and distribution of topical diseases (WHOCC, 2015). Nonetheless, it is important to mention that clotrimazole and terbinafine have been included in the list of top ten chemical substances targeted for future screening (Hilton et al., 2003).

3.3.3 PCP Usage

Participants reported the use of 54 assorted brands of PCPs, which were grouped into 15 product categories and the data show a wide variation in use amount among different products (Table 3. 2). The survey estimated that each household consumed approximately 60.8 Litres of a variety of PCPs per year and cleaning products accounted for approximately 47% of this volume. Household pesticides were the most consumed PCPs, with mean annual use of 9.6 litres per household. The high reported use (95%; n=325) of household pesticides is understandable, given that in many developing countries, pesticides are often used to control a variety of household pests, such as fleas, bugs, cockroaches and mosquitoes.

Table 3. 1 Estimated API Use in southern Nigeria, Days of Therapy and ATC Classification

ATC code	ATC Main group	ATC category	ATC Drug Name	WHO DDD (grams)	Number of Users	Days of Therapy (DOT)	Average API use (grams) Capita^{-1} year^{-1} (2016)	Extrapolated API use (Kg) (southern Nigeria) (2016)
N02BE01	Nervous system	Analgesics	Paracetamol	3	306	10812	92.7	3150780.00
NO2BB02	Nervous system	Analgesics	Metamizole sodium	3	15	1036	8.88	301920.00
M01AE01	Musculo-Skeletal system	Anti-inflammatory	Ibuprofen	1.2	6	240	0.823	27880.00
P01BA01	Anti-parasitic	Antimalarial	Chloroquine phosphate	0.5	19	308	0.44	14960.00
P01BC01	Anti-parasitic	Antimalarial	Quinine Sulphate	1.5	45	772	3.31	86700.00
P01BF01	Anti-parasitic	Antimalarial	Artemether & Lumefantrine	0.28	242	3872	3.10	105400.00
P01BE03	Anti-parasitic	Antimalarial	Artesunate	0.28	39	484	0.39	13260.00
J01CA01	Anti-parasitic	Antibacterial	Ampicillin	2	188	3144	18.0	610640.00
J01AA07	Anti-infective	Antibacterial	Tetracycline	1	27	548	1.57	53380.00
J01MA02	Anti-infective	Antibacterial	Ciprofloxacin	1	62	928	2.65	90100.00
J01CF02	Anti-infective	Antibacterial	Cloxacillin	2	106	1952	11.2	379100.00
J01EC01	Anti-infective	Antibacterial	Sulfamethoxazole	2	40	576	3.29	111860.00
JO1EA01	Anti-infective	Antibacterial	Trimethoprim	0.4	40	576	0.66	22440.00
R05CA03	Respiratory System	Cough & cold preparations	Guaifenesin	0.9	149	3804	9.78	332520.00
R01BA52	Respiratory System	Nasal Decongestant	Pseudoephedrine	0.24	74	1712	1.17	39780.00
R06AX07	Respiratory System	Nasal Decongestant	Triprolidine	0.0075	74	1712	0.037	1360.00
R05DA09	Respiratory System	Cough & Cold suppressants	Dextromethorphan	0.09	149	3804	0.978	32980.00
R06AA02	Respiratory System	Antihistamines	Diphenhydramine	0.2	198	4480	2.56	87040.00

ATC-Anatomical Therapeutic Chemical; DDD-Defined Daily Dose; DOT-Days of Therapy; API-Active Pharmaceutical Ingredient

In addition, in malaria endemic countries, insecticide residual spraying is a widely recommended approach for the control of mosquitoes , a major household pest, which presents serious public health challenges (Autino et al., 2012). In a similar study, it was reported that individuals in UK consumed about 33 Litres of PCPs per year, with several down-the-drain products such as dishwashing liquids and handwash gels accounting for 40% of this volume (Rotsidou and Scrimshaw, 2015).

We identified 26 active ingredients from the assorted product brands and the estimated quantities consumed annually per household varied widely and ranged from 4.7 litres (Linear alkylbenzene sulfonate (LAS), a surfactant), to 0.00010 litres (cyfluthrin, a pyrethroid insecticide) (Table 3.2.). The relatively high estimated use of surfactants is not surprising as many product brands (e.g. laundry detergent and dishwashing liquids) contain both anionic surfactants (e.g. LAS, alcohol ethoxylate (AEO); alkyl ethoxy sulphates (AES) and non-anionic surfactants (e.g. alcohol ethoxylates, (AE)). There is therefore the potential for broad-scale release of surfactants into the environment as components of domestic wastewater.

Table 3. 2 Estimated annual PCP use by category in southern Nigeria, functions and active ingredients

PCP category	Average PCP use (Liters $HH^{-1}yr^{-1}$)	PCP Active Ingredients (AI)	Functions/Uses	No. of users (n)	Min AI use (Liters $HH^{-1}yr^{-1}$)	Max AI use Liters $HH^{-1}yr^{-1}$)	Average AI use Liters $HH^{-1}yr^{-1}$)
Household pesticide	9.6	LAS	Surfactant	350	2.22	7.1	4.7
Anti-bacterial soap	6.4	Sodium Laureth Sulfate	Surfactant	350	0.85	3.9	2.6
Detergents	4.6	Sodium palmate	Cleansing agent	211	0.27	3.3	1.5
Laundry Bar soap	4.1	Alcohol Ethoxylate	Surfactant	350	0.46	2.4	1.3
Bleach	4.5	Alcohol Ethoxy Sulfate	Surfactant	350	0.47	2.4	1.3
Dishwashing Liquid	4.8	Sodium Cocoate	Cleansing agent	211	0.19	2.2	0.9
Dishwashing Bar	2.9	Dichlorvos (DDVP)	Organophosphate insecticide	190	0.19	1.4	0.9
Body Lotion	3.9	Cresol	Antibacterial agent	89	0.73	1.3	1.1
Toilet soap	3.6	Chloroxylenol	Antiseptic/disinfectant	340	0.12	1.1	1.1
Toothpaste	3.0	Sodium hypochlorite	Bleaching agent	198	0.16	0.5	0.35
Deodorizer	3.0	Glycerine	Moisturizer	100	0.21	0.3	0.26
Shampoo	2.6	Aluminum Chlorohydrate	Antiperspirant	150	0.10	0.2	0.16
Antiseptic Liquid	2.6	Chlorhexidine	Disinfectant/Antiseptic	89	0.07	0.18	0.16
Germicide	2.1	Ammonium thioglycolate	Hair perm	120	0.05	0.089	0.076
Hair perm	1.5	Cetrimide	Antiseptic	89	0.0040	0.080	0.059
Deodorant	1.6	Hydroquinone	Skin-lightening agent	141	0.0050	0.066	0.025
		Triclosan	Antibacterial / antifungal	340	0.0030	0.030	0.016
		Triclocarbanilide	Antimicrobial/antifungal	200	0.0040	0.030	0.018
		Phenothrin	Aerosol insecticide	35	0.011	0.019	0.015
		Transfluthrin	Pyrethroid insecticide	50	0.0010	0.0040	0.0030
		Permethrin	Pyrethroid insecticide	50	0.0010	0.0030	0.0020
		Tetramethrin	Pyrethroid insecticide	30	0.00010	0.0010	0.00070
		Deltametrin	Pyrethroid insecticide	30	0.000040	0.00030	0.00020
		Imiprothrin	Pyrethroid insecticide	20	0.00020	0.00030	0.00030
		Prallethrin	Pyrethroid insecticide	20	0.00020	0.00020	0.00030
		Cyfluthrin	Pyrethroid insecticide	20	0.00010	0.00010	0.00010

PCP-personal care product; AI – Active ingredient; HH – Household; LAS - Linear alkylbenzene sulfonate; DDVP - 2,2-dichlorovinyl dimethyl phosphate

3.3.4 Disposal practices for PPCPs

Consistent with the wider literature (Daughton and Ruhoy, 2009; Ekedahl, 2006; Braund et al., 2009), our findings show that medicines are stored at home and unused medications are eventually discarded by various routes (Figure 3.3). Seventy-five percent (n = 263) stored medicines at home and analgesics represented the highest share (46.6%, n = 123) of stored medications, followed by antimalarial agents (22.3%, n = 59), vitamins (14.3%, n = 38), antibiotics (12.9%, n = 34) and antifungals (0.6%, n = 2). Our results are consistent with earlier studies, which reported analgesics as the most commonly stored medicines among university students in Jos, Nigeria (Auta et al., 2012). Regarding current disposal practices of PPCPs, over 80% of participants discarded unwanted medications and PCPs together with household wastes, while relatively fewer (<11%) participants discarded through sewerage (e.g. toilet/sink) (Fig.3.1). We recorded no responses for the 'return to pharmacy' disposal route, which is not surprising, considering that formal medicine takeback programs have not been implemented in Nigeria. Disposing of leftover medications with household waste is not peculiar to the study area. A recent review of global disposal practices of unused medicines found garbage disposal to be a leading method of disposal of leftover medications (Kusturica et al., 2015). While it has been argued that garbage disposal may be an effective way to reduce the load of pharmaceuticals in wastewater systems (Glassmeyer et al., 2009), the consequences of Nigerian households storing medications and eventually discarding unused medications in garbage bins may be noteworthy. Besides the economic burden associated with pharmaceutical waste (Kümmerer, 2008), poorly stored medicines are prone to quality deterioration and ultimate loss of potency when exposed to unfavourable conditions such as air, humidity, heat and sunlight (Temu et al., 2006). Thus, we envisage that the bright, humid and hot climatic conditions in Nigeria may favour the deterioration in quality of improperly stored medications. It is therefore imperative that awareness is created among end-users about the potential dangers of improperly stored medications. Furthermore, APIs disposed of as household waste ultimately become part of landfill leachates (Slack et al.,

2005), which can potentially contaminate unprotected aquifers and surface waters downgradient of municipal landfills (Barnes et al., 2004; Kümmerer, 2008). This poses a threat to human and environmental health, especially in many developing countries where urban waste is managed in poorly engineered landfills (Kusturica et al., 2015). In Nigeria, solid waste generation is on the increase with increasing population growth, and these wastes are predominantly managed in open dumps. Besides the potential threats to nearby water supplies, open dumps expose scavengers to leftover medications, which as earlier discussed, may likely increase the risk of abuse and diversion.

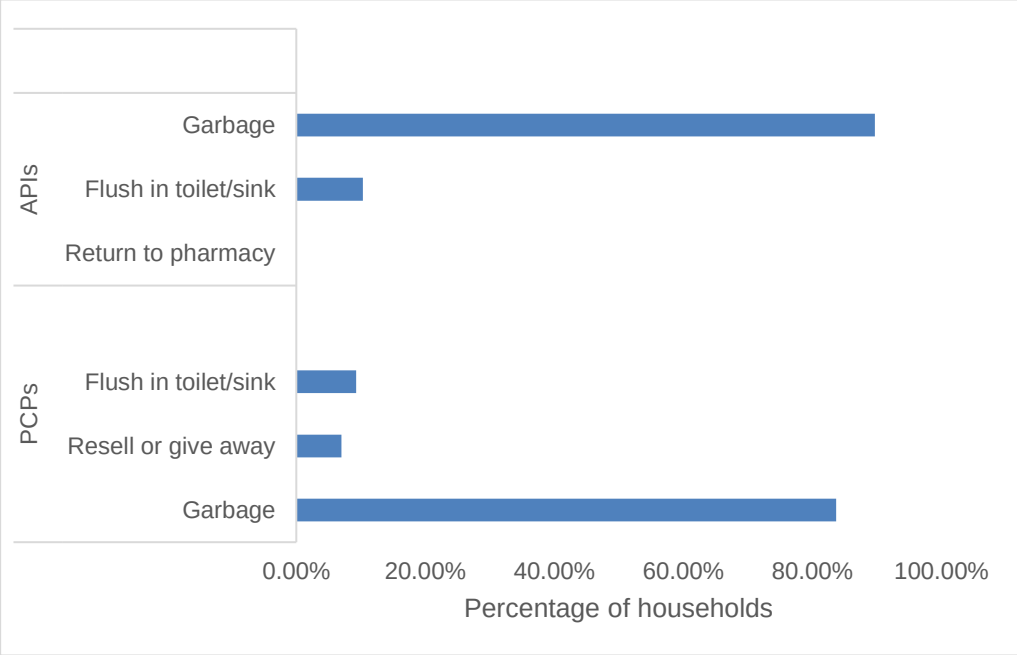


Figure 3. 1 Percentage disposal of PPCPs by route

3.3.5 Pro-environmental attitudes and WTP for groundwater protection program

Most participants (97.3%; n = 341), indicated that protecting the environment and keeping it in a good state was a personal responsibility, and some participants strongly agree that under the right conditions, they would engage in pro-environmental behaviours such as recycling more if convenient recycling facilities were available (42.3%; n = 144) and would properly dispose of household wastes if there were convenient places to take them (47.4%; n = 161). Over 80% (n = 282) of participants were very or extremely concerned about possible contamination of domestic water wells by septic systems and 60% (n = 210) were very concerned about water pollution in general. When asked if they would be willing to participate in a medicine takeback program, 315 participants (90%) reported it was very or extremely likely that they would return unwanted medicines to local pharmacies for safe disposal. However, nearly two-third (61.7%; n = 216) of participants would be willing to pay a fee to support groundwater protection program, and among these, 43% (n = 153), would pay the lowest monthly offer value (500 – 2000 naira; $2 - $8 USD), whereas less than 7% (n = 23) would be willing to contribute the highest range of fees for groundwater protection (Figure 3.2). This is consistent with the demand theory, which assumes that the higher the price of a good, the lesser the demand for that good. Elicited value was zero for 136 participants (38.9%) who would not be willing to pay a fee. Thus, the estimated monthly mean WTP for groundwater protection program was 1946.7 naira ($7.8 in 2016 dollars), with 'protest zeros' excluded. It is interesting, however, that over one-third (38.9%; n = 136) of responses are classified as 'protest-zero'. With respect to reasons for objecting to pay a fee, nearly half of the so-called 'protestors' wanted 'the government to bear the cost'; 18 participants (5.1%) doubted the scheme would actually take place; 31 participants (8.9%) claimed they could not afford to pay; 17 participants (4.9%) believed they pay enough taxes already; 3 participants (0.9%) had ethical objections to personal payment for a public good, and 2 participants (0.6%) claimed they do not use groundwater as a source of water supply.

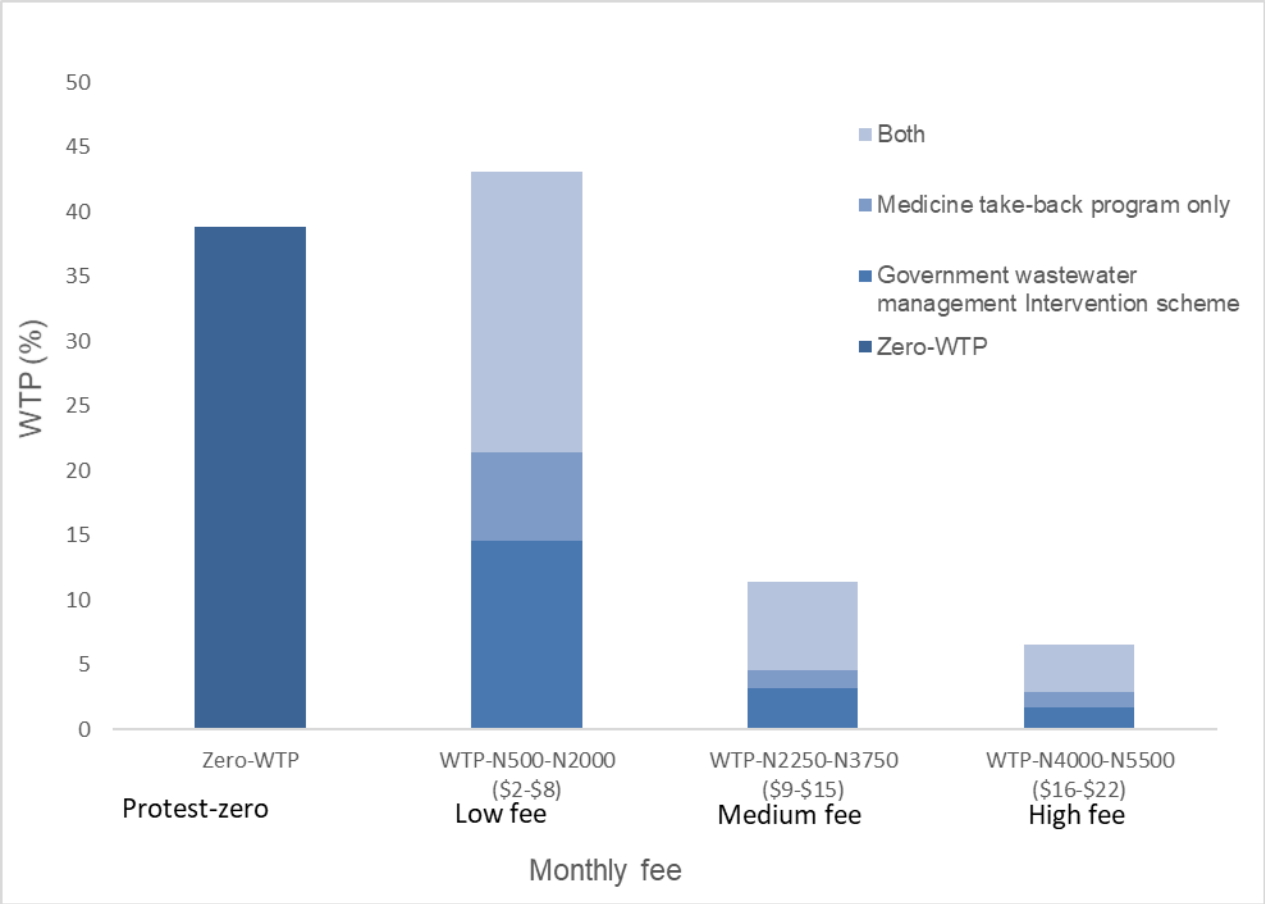


Figure 3. 2 Percentage distribution of WTP for groundwater protection program by fee category

The zero-bid behaviour is not uncommon for CVM studies, particularly when applying the open-ended or payment card elicitation approach (Cho et al., 2005). It has also been suggested that there is often a proportion of individuals who will not value a proposed change in some attribute of an environmental good (Jorgensen and Syme, 2000). Similar reasons for negative WTP were reported by Lorenzoni et al. (2007), who identified scepticism, distrust in government authorities, externalizing responsibility and blame, amongst others, as barriers to public engagement with climate change among the UK public. These findings suggest that zero WTP is not only an issue of affordability but could be influenced by political and other non-monetary factors.

3.3.6 Predictors of WTP for groundwater protection program

Linear regression analyses predicting association between pro-environmental attitudes and willingness to participate in groundwater protection program (Table 3.3) demonstrated that 'concern for risk of groundwater contamination' and 'perceived personal responsibility to protect the environment' had statistically significant ($p < 0.05$) impact on participation behaviour.

Table 3. 3 Logistic regression analysis of predictors of willingness to participate in groundwater protection program

Variable	B	SE	Exp (B) (OR)	95% CI	*p*-Value
Constant	-2.344	.761	0.096	-	-
Concern for risk of groundwater contamination	.336	.115	1.399	1.117 - 1.753	0.004
Perceived personal responsibility to protect the environment	.344	.153	1.411	1.045 - 1.905	0.022
Need of government policies for environmental protection	.200	.138	1.221	0.932 - 1.600	0.147
Need of modern waste management facilities	.243	.182	1.276	0.893 - 1.823	0.181

Dependent variable (Willingness to participate in groundwater protection program for a fee); S.E (Standard Error); OR (odds ratio); CI (Confidence interval).

Examination of the regression coefficients based on beta weights shows that a one level increase in perceived personal responsibility to protect the environment increases the odds of participation in groundwater protection program by 41% (OR = 1.411; p-value = 0.022). Similarly, a one level increase in concern for risk of groundwater contamination increases the odds of participation by 39% (OR = 1.399; p-value = 0.004). This is consistent with a study which found attitudinal behaviours, specifically concern for the environment, to be strongly associated with WTP for green electricity (Rowlands et al., 2003).

The multinomial logistic regression model also shows a significant positive association between the amount participants would be willing to pay and male gender, household income and level of education completed (see the Appendix for Tables A.B3 – A.B6). As household income increases

by one level, it is 41% less likely that households would choose the low fee range compared to the high fee range (p-value = 0.0001; OR = 0.593; CI = 0.482 - 0.731). This effect is consistent with the economic theory which suggests that a rise in income will result in a WTP for more goods or a service. We also found statistically significant (p-value = 0.032) effect of level of education completed on WTP amount. As education completed increases by one level, the odds of participants selecting low fees rather than high fees decrease by 57% (OR = 0.430; CI = 0.256 - 0.722); this is possibly due to greater levels of risk awareness or higher level of concern for groundwater quality in more educated households. There was also, a statistically significant (p-value=0.023) relationship between male gender and WTP amount. We found that men compared to women were 66% (OR = 0.340; CI = 0.132 - 0.874) less likely to choose low fees than high fees. The greater potential to choose low fees by women may reflect the cultural values in many developing countries. It has been claimed that most women in many developing countries do not control household finances, and as such, there is often an imbalance in resource distribution between men and women (Quisumbing, 2003). Hence, the female participants in this study may have been handicapped to choose a high fee value, particularly if it would affect the overall household expenditure. In a similar study eliciting WTP for health insurance in Nigeria, it was found that female headed households were willing to pay lesser amounts than their male counterparts (Ataguba et al., 2008). We found no statistically significant (p-value = 0.755) relationship between age of participants and WTP amount, but for an additional year in age, there will be a 6.9% (OR = 1.069; CI = 0.702 – 1.630) increase in the probability that a participant will be in the low rather than the high fee range.

3.3.7 Strength and limitations of the study

3.3.7.1 Response rate

Although web-based surveys represent a cheap (in terms of both time and cost) and efficient (in terms of completion) way of collecting data (Bucevska, 2000), our study showed relatively lower participation from web questionnaires (n = 57) compared with the paper questionnaire (n = 293). This supports the claim that response rates are often lower in web-based surveys compared with other modes of data collection (van Gelder et al., 2010). We attribute the low response rate to the limited access to and high cost of online services in the study area. Equally restrictive, was the inability to establish the online response rate, due to the recruitment method for online participants, which was open to the public via various online recruitment platforms, with no definitive sample group. Previous studies have also reported the difficulty in establishing online participation rates with open recruitment strategy (van Gelder et al., 2010).

3.3.7.2 Representativeness

To achieve our goal of a representative national sample, we adopted a mixed mode approach, which combined web-based questionnaires with household self-administered questionnaires. We also applied a stratified random sampling technique in areas potentially representative of many urban and rural settings across the country, and as such, we believe that the usage patterns of PPCPs reported in this study are representative of the Nigerian population and there was no indication for selective non-response. However, the highly educated respondents (60%) in our sample may be slightly overrepresented compared with the literacy status of the Nigerian general population. Furthermore, we acknowledge that due to the influence of certain region-specific factors (including income, population characteristics, culture, climatic conditions, and family size) on shopping habits, purchasing behaviour and product brands (Rani, 2014), it may be difficult to generalize our findings to other populations, particularly, those in high income economies. However, it is important to mention that our questionnaire format is versatile, and could be

implemented in many countries, particularly the African developing region, to assess PPCP usage and disposal pattern, pro-environmental attitudes and WTP for environmental goods.

3.3.7.3 Recall issues

The survey required respondents to recall their use of PPCPs during the previous year. With this relatively long time frame, we were concerned about respondents' ability to accurately recall PPCP use. Stone and Shiffman (2002) agree to the potential for distortion caused by recall bias whenever information of past experiences are elicited directly from respondents. In this regard, we acknowledge the possibility of recall bias and therefore cannot tell how well our survey participants recalled use (in terms of type, amount and frequency), and as a result, it is difficult to ascertain whether respondents were systematically underreporting or overreporting use. This possibility may place a range of uncertainties around our estimates of product use and requires cautious interpretation of result estimates. Nonetheless, it has been argued that both sources of error (i.e. underreporting and overreporting bias), might in the long run, neutralize one another (Biesterbos et al., 2013). On this account, we assume that overall, the estimated average annual use amount of PPCPs reported in this study may mirror actual usage in Nigerian households.

3.4 Conclusion and Recommendation

The focus of this study was to address a broad range of issues regarding consumption of PPCPs, current disposal routes for leftover medications and personal care products and eliciting the willingness to pay a fee for future groundwater protection program. Some of these issues have not been raised or answered conclusively in previous research in the study area. The lack of usage data on API use has been highlighted as one of the major data gaps regarding pharmaceutical use globally (Monteiro and Boxall, 2010), and we have demonstrated that questionnaire data can be used as a proxy to measure usage, and have provided information regarding PPCP usage pattern, by type and mass in southern Nigeria. This study therefore,

provides a reference point for future studies to analyse trends in API consumption pattern, particularly in developing countries. API use amount varied considerably, but because we have not measured the adequacy of consumption, it is not clear if amounts consumed reflect patient needs. It is therefore imperative that safe and appropriate sale of medicines are a consideration in healthcare policy decisions in Nigeria. Enforcing legislations that will restrict over the counter sale of medicines like antibiotics would be a good starting point, as self-medication is widely practised in the study area. Over 80% of households discard unwanted medicines and PCPs with household waste and there is currently no medicine take-back program. Under this current disposal scenario, there is little scope for reductions in the input of pharmaceuticals to landfills since disposal to trash would remain the most viable option available to households. In this regard, there may be need to embrace other strategies such as the 'upstream green approach' with even greater potential to lessen the accumulation of leftover medications and the subsequent need of disposal (Daughton and Ruhoy, 2008). Although a high proportion of participants would be willing to participate in the proposed groundwater protection program, most participants would be willing to pay low fees to support such a program. Our findings suggest that only educated males from households with high income would be more likely to pay high fees than low fees for the groundwater protection program. This raises questions about funding and whether the population in general can afford such a program or whether such programs should be funded exclusively by the government or the pharmaceutical industry or both as a subsidized service. The most commonly used PPCPs identified in this survey are likely to be emitted to the environment, primarily through the onsite treatment and disposal systems. In the next section, the APIs and PCP active ingredients would be prioritized to determine the compounds with the greatest potential to enter groundwater to inform future groundwater monitoring campaigns in these communities and perhaps across the nation.

Chapter 4

Risk-based prioritization of pharmaceuticals and personal care products for groundwater monitoring in non-sewered communities

4.1 Introduction

This section describes the methodology to prioritize PPCPs for groundwater monitoring in unsewered communities in southern Nigeria. As a vital component of life, the persistence of PPCPs, even at low doses in water systems raises concerns over the potential human health risks arising from exposure through drinking water intake (Carrara et al., 2008; Godfrey et al., 2007; Kolpin et al., 2002; Petrović et al. 2003). PPCP entry into the drinking water sources occurs mainly through wastewater treatment processes, which have been recognized as a significant exposure pathway that conveys human use pharmaceuticals into the environment (Boxall et al., 2012). This occurs when consumers either excrete the fraction of APIs not utilized by the body after therapeutic use in urine and faeces (Daughton and Ternes, 1999; Boxall et al., 2012), or improperly discard leftover medications into toilets or sinks (Glassmeyer et al., 2009).

Complete removal of PPCPs is rarely achieved during wastewater treatment (Conn et al., 2006) and, while some of these substances may be rapidly degraded and mineralized, (Gottschall et al., 2012), most are not readily biodegradable (Halling-Sørensen et al., 1998). Hence, with continuous introduction into the waste stream following routine use (Monteiro and Boxall, 2010), these substances can persist in wastewater effluent or accumulate in sludge (Conn et al., 2010).

In areas without sewer connectivity, wastewater treatment and disposal pose a threat to groundwater resources (Carroll et al., 2006), as partially treated effluent continuously infiltrates through the soil to underlying aquifers which are often used as a source of drinking water (Carrara et al., 2008; Phillips et al., 2015). In this regard, there has been an increased need to characterize septic effluent quality (Conn et al., 2006; Phillips et al., 2015), and assess the potential human

health risks from exposure to wastewater borne contaminants, particularly PPCPs and other chemicals of emerging concern (Carrara et al., 2008).

Several studies have reported the presence of a variety of PPCPs in septic effluents, and their concomitant occurrence in groundwater recharged by these systems (Hinkle et al., 2005; Verstraeten et al., 2005; Godfrey et al., 2007; Swartz et al., 2006; Carrara et al., 2008; Schaider et al., 2014; Phillips et al., 2015). Despite the predominance of septic systems in many low to middle income countries, most of these studies have been conducted in developed countries, and it has been widely acknowledged that research on emerging contaminants remains low in developing countries, particularly in the African region (Sorensen et al., 2014); it is expected that with increasing population growth and resultant disease burden, such regions are likely to utilize and discharge more APIs to the environment than in high income countries (Kookana et al., 2014).

Evidence that low-level occurrence of PPCPs can cause acute harm to ecosystem and human health is limited; however, the risk of effects due to chronic exposure are expected (Jjemba, 2006). Moreover, these compounds occur in the natural environment as mixtures of dozens of compounds and the influence of additive or synergistic effects of constituent mixtures are only beginning to be elucidated (Richardson et al., 2005). There is also an increased level of concern that the accumulation of PPCPs in drinking water can potentially affect human health, even though these effects have not been fully examined and remain uncertain (Cunningham et al., 2009). Prior to the issuance of Directive 2013/39/EU of the European Union amending earlier directives on priority substances in the field of water policy (European Commission, 2013), maximum safe contaminant levels for emerging contaminants in drinking water were not defined under any statutory regulations. The lack of regulation results from a paucity of toxicological evidence related to pharmaceutical exposure from drinking water (Straub & Hutchinson, 2012). Furthermore, little is known regarding the fate and behaviour of APIs in the environment, partly because, only a

handful of the numerous APIs currently in use have been investigated and have experimental data on environmental levels, fate, and effects (Al-Khazrajy and Boxall, 2016).

The time and costs associated with monitoring the vast number of APIs released into the environment have motivated the use of prioritization to identify substances in use that may pose the greatest risk to human health and the environment (Boxall et al., 2012). This approach allows substances to be ranked according to their potential impacts, so that available resources, can be focused on substances that may pose the greatest risk to ecological and human health.

Several attempts have been made to rank and estimate the risks posed by anthropogenic chemical compounds in the environment using multiple criteria and ranking approaches. Prioritization efforts have been conducted for various water sources (e.g. surface water, groundwater, and finished drinking water) and have been conducted in the United States (Kumar and Xagoraraki, 2010); South Korea (Kim et al., 2008), the United Kingdom (Boxall et al., 2003; Capleton et al., 2006; Guo et al., 2016); Europe (Besse and Garric, 2008; Kuzmanović et al., 2015); and China (Yu et al., 2014; Kong et al., 2016). The approach adopted in most studies has been based on predictions of exposure and toxicity, as this strategy, allows the prioritization schema to be applied to the numerous compounds in use that have limited data (Boxall et al., 2012). Nonetheless, several authors have highlighted that prioritization research, which is currently focused on developed economies, particularly North America and Europe, has resulted in limited information about priorities in other geographical regions of the world (Burns et al., 2018; Al-Khazrajy and Boxall, 2016). These authors suggest that the lack of data availability (e.g. information on API usage) in many developing regions challenge research efforts and is partly to blame for this this research bias, evidenced by the low number, type and quality of research outputs focused on these regions.

Of the few investigations on the impact of septic systems on groundwater resources in Nigeria, most have often focused on identifying conventional wastewater contaminants, particularly microbial contamination (Farouq et al., 2018; Eze and Eze, 2015; Fubara-Manuel and Jumbo, 2014). The occurrence of residues from widely used PPCPs has hardly been characterized, and therefore, the risk of exposure to potentially harmful emerging contaminants via drinking water has also been consistently overlooked. It has been recognized that understudied areas, such as Nigeria with large urban populations and no sewer connectivity may be hotspots of pharmaceutical exposure and risk (Burns et al., 2018).

The aim of the present study was therefore to establish the importance of PPCP exposure as a burden on groundwater systems in Nigeria, and to provide a screening tool for assessing groundwater contamination potential of a variety of PPCP residues in septic effluent to inform future monitoring protocols. The prioritization approach used was designed to identify PPCPs with the greatest potential to enter the underlying aquifer recharged by septic systems in southern Nigeria, where no information currently exists concerning exposure and potential effects of these emerging pollutants. Because limited data availability often introduces huge uncertainties while using comprehensive exposure models, we employed a simple risk index approach as a screening tool, which required evaluating usage data, environmental characteristics and the toxicological profile of individual APIs and PCP active ingredients.

4.2 Prioritization approach

The prioritization approach involved the use of a ‘risk index’ for the pre-selection of PPCP residues with the potential to enter groundwater affected by onsite wastewater treatment processes. The prioritization scheme was inspired by the work of Sinclair et al. (2006), who developed a screening approach for the pre-selection of pesticide transformation products in drinking water sources affected by agricultural activities. The prioritization scheme broadly considers factors which will

determine the impact of a PPCP residue on drinking water supply (i.e. source water) such as 1) its potential to enter the environment; 2) its treatability in drinking water utilities and 3) its potential effects on human health. The risk-based prioritization approach illustrated in Figure 4.1, demonstrates the prioritization criteria using a combination of exposure and effects measures, and comprises three key stages: exposure, toxicity, and treatability

First, exposure to PPCP residues relates to the assessed potential of a PPCP residue to enter the environment following the use of PPCPs in households and the subsequent discharge of contaminated wastewater via septic systems, which is estimated using available data on key exposure parameters - usage amount, mobility and persistence. Exposure was characterized according to a ranking methodology, which provides a normalised value for three exposure criteria: usage, sorption and degradation, and likely values for each determinant of exposure lie between 0 and 1. Thus, the output is not represented by predicted environmental concentrations (PECs) of PPCPs in source water, but by a ranking of a PPCP residue relative to other PPCP residues identified within the evaluated media or system (e.g. groundwater). In this context of relative ranking, the underlying assumption is that compounds with high usage amounts, less preference for the solid phase (e.g. suspended solids, sediment or soil) and high resistance to degradation will be more likely to migrate to source water. Second, potential human health effect which relates to the likely consequences to human health from chronic low-level exposures to PPCPs through drinking water consumption was determined by using acceptable daily intakes (ADIs), as these are derived on the basis that repeated exposure over a lifetime will amount to no risk of harm to the general population.

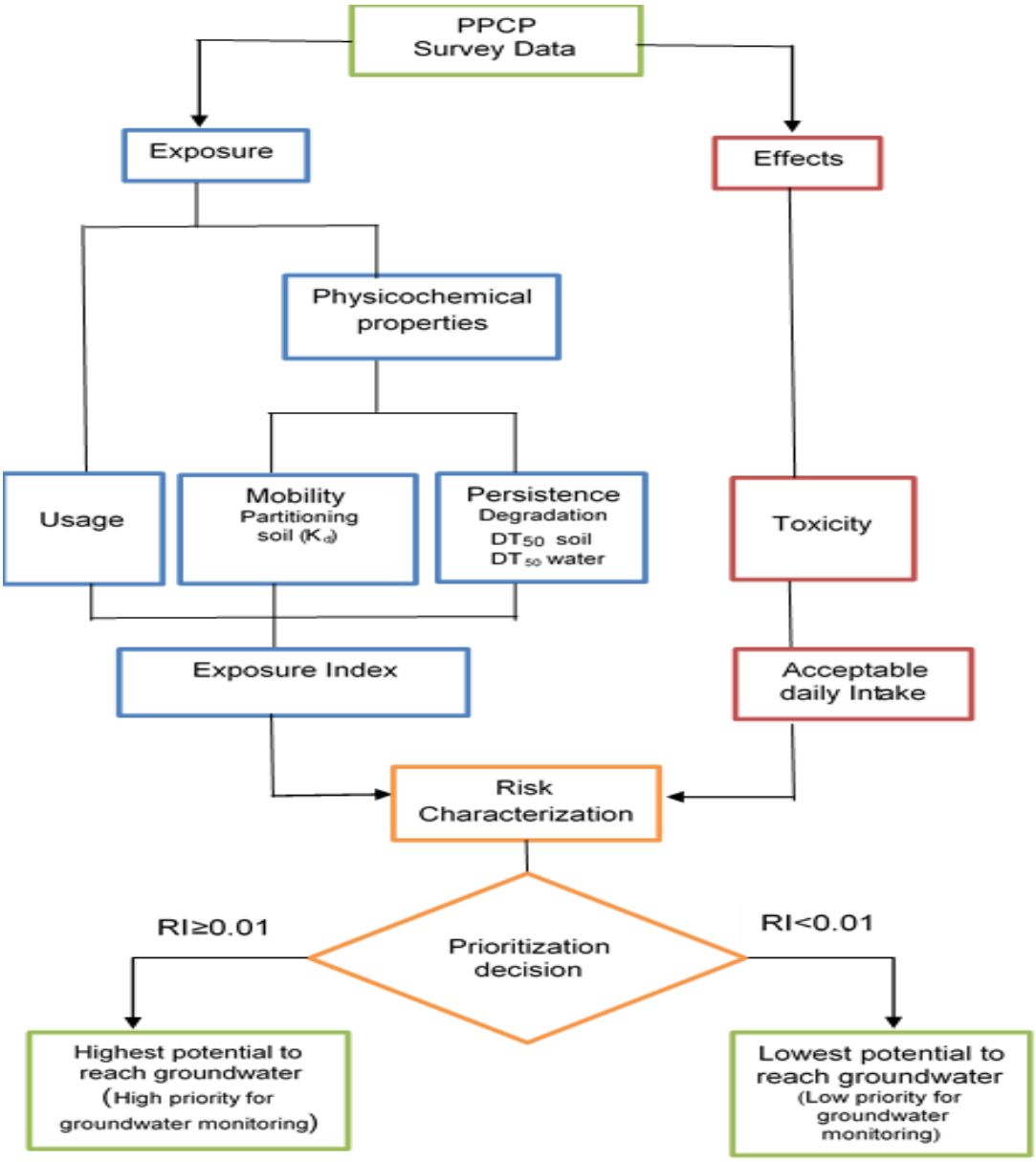


Figure 4. 1 Schema for prioritizing PPCP residues for groundwater monitoring campaign in non-sewered communities

PPCP – pharmaceuticals and personal care products; RI - Risk index; K_d - Distribution constant or partition ratio; DT_{50} soil - Degradation Half-life in soil; DT_{50} water - Degradation Half-life in water; Survey data - 2016 survey of household use of PPCPs in southern Nigeria.

Finally, a risk index (RI) was derived by comparing the exposure index to the ADIs to rank the potential risk posed by PPCP residues in source water. The higher the RI values obtained, the higher the potential for the PPCP to enter groundwater recharged by septic systems.

Treatability of source water prepared for human consumption in drinking water utilities will determine the extent to which contaminants will be present in the finished drinking water (Stackelberg et al., 2007). However, in the context of the current study area, water treatment is unavailable and therefore treatability has been excluded from consideration. It should be noted that the focus of this study was restricted to the potential human health consequences arising from indirect chronic low-level exposure to PPCPs in groundwater. Other possible exposure pathways such as nearby surface water bodies, which may be recharged by contaminated aquifers, and non-target organisms (e.g. earthworm), though relevant, were not considered in the present analysis.

4.2.1 Estimating exposure

The potential for PPCP residues in septic effluent to reach the underlying aquifer will depend on a wide range of factors, but in the present scenario, exposure was approximated by a simple exposure model that included three exposure determinants: 1) usage amount, 2) sorption and 3) environmental half-life. These data help to approximate the amount of each PPCP potentially reaching groundwater through septic systems, their mobility in the subsurface and persistence in the environment. Reductions resulting from treatment in septic systems were not considered as removal efficiency data for most APIs do not exist and excluding these removals represents a conservative approach that is protective of human health.

4.2.1.1 Usage

Inclusion of usage as a criterion is based on the premise that when APIs are consumed, a portion is utilized or metabolized in the human body, and the rest is excreted in urine and faeces.

Likewise, active ingredients in PCPs are released into the environment following bathing and showering and disposal unwanted items. In many prioritization studies, usage can be estimated from prescription data or manufacturing and import data (Kostich et al., 2010). However, due to a lack of countrywide prescription data as well as the manufacturing and importation volumes of APIs, coupled with limited access to marketing data for consumer products, data on PPCP usage were gathered from a household survey of use and disposal patterns of PPCPs in Nigerian households (as previously discussed in Chapter 3). Thus, the geographical scope of this prioritization scheme is a region of approximately 32 million inhabitants in southern Nigeria. Furthermore, the research scope was limited to the screening of parent compounds and excluded metabolites and transformation products (TPs). Nevertheless, it is recognized that some TPs may be more toxic than their parent compounds (Boxall et al., 2004), but limited data availability on TPs of emerging contaminants at environmental levels restricted the consideration for TPs in this assessment.

Using the PPCP usage data, an index (A) that reflects the amount of PPCP that will be released into the geographical area where these products are used was calculated using Equation 4.1

$$A = \frac{U}{Umax} * (1 - f) \qquad (4.1)$$

where A = the PPCP amount index; U = the total mass of the PPCP used in the geographical area over a specified period (e.g. kg yr^{-1}). U_{max} = the total mass of the highest used PPCP in the geographical area over a specified period (e.g. kg yr^{-1}), and *f* = the maximum fraction of transformation product formed within the environmental compartment of interest. *f* value was set to zero to reflect the assumption of no degradation in this step.

4.2.1.2 Mobility

Once released into the surrounding soil environment, septic effluent will infiltrate into the subsurface, and the potential for persisting PPCPs in septic effluent to migrate to the underlying aquifer will be influenced by many factors, notably, their affinity to solid phases (e.g. soil / sediment) (Conn and Siegrist, 2009). Sorption to soil is therefore a vital process in the fate and transport dynamics of chemical compounds as they percolate through the soil (Roberts et al., 2014). Hence, in this prioritisation scheme, mobility characterisation involved the evaluation of the sorptive behaviour of individual PPCPs, described by the distribution coefficient (K_d), a parameter, which measures the partitioning of a compound between soil/sediment and aqueous phases (Grathwohl, 1990). The utility of K_d in predicting the fate and the migration potential of substances in the subsurface has been well documented (Sheppard et al., 2009). In stage 2 of the exposure assessment, the mobility index (F) was calculated using Equation 4.2 and represents the fraction of the PPCP residue that is likely to remain in the aqueous phase and therefore has the potential to migrate to groundwater.

$$F = \frac{1}{1 + K_d\, r_{sw}} \qquad (4.2)$$

Where F = the mobility index, K_d = the distribution coefficient for adsorption ($cm^3\ g^{-1}$) and r_{sw} = ratio of the solid phase mass to aqueous-phase volume of the environmental compartment of interest. Given that the sorptive behaviour of a compound is strongly influenced by the organic carbon content of the soil / sediment, sorption can be normalised to organic carbon content (OC%) of the soil/sediment, to give the organic carbon normalised coefficient (K_{oc}), which in turn strongly correlates with respective octanol-water partition coefficients (K_{ow}), and is often considered to be fairly constant, regardless of the nature of the soil or sediment sample (Grathwohl, 1990). Hence, if K_d values are not available, several empirical relationships can be used to estimate sorption from K_{ow} and the soil organic carbon content (Piwoni and Keeley, 1990). In the absence of total

organic carbon content (TOC) values for a given soil, a TOC of 2% can be used as a default value as proposed in the European Chemicals Bureau Technical Guidance Document on Risk Assessment (TGD) (European Commission, 2003).

Besides sorptive behaviour (e.g. K_{oc}), migration of PPCP residues to source water will be influenced by the extent of exposure to sorptive material (e.g. soil and sediment). Hence, PPCP residues in septic effluent discharged into the subsurface environment will be exposed to relatively more sorptive material than effluent discharges that do not involve soil compartment (e.g. direct discharge to surface water). Therefore, for the onsite treatment of wastewater involving effluent release to the surrounding soil environment, r_{sw} value of 7.5 was adopted, based on the standard environmental characteristics (e.g. volume fraction of solids in soil (0.6 m_{solid}^3 m_{soil}^{-3}); volume fraction of water in soil (0.2 m_{water}^3 m_{soil}^{-3}); density of the solid phase (2500kg_{solid} m_{solid}^{-3}) for agricultural / soil application of pesticides proposed in the TGD on risk assessment (European Commission, 2003). It needs to be said that there are limitations in the use of the parameters proposed in the EU TGD to determine the mobility index in the current study, given the differences in climatic conditions between the EU and the study area (Nigeria). Nigeria as a country in the tropics, is in the warm and humid region, with two distinct seasons- dry and rainy season (Ajibola, 2001). These conditions (temperature and rainfall) are known to induce changes in soil properties, including losses in organic carbon fractions of soil systems (Biswas et al., 2018), which play a significant role in the sorption of soil pollutants (Qi et al., 2017) and hence its mobility in the soil. Hence, the use of generic soil parameter values from a temperate region to characterize the mobility potential of contaminants in soil from a tropical region may be misleading, given the variation in the characteristics of the two environments both in time and space. However, given that the K_d values used in Equation 4.2 to estimate the mobility index were estimated from K_{ow} values (of individual compounds), which are often considered to be fairly constant, and not influenced by the nature of the soil (Grathwohl, 1990), it is assumed that the use of default soil

parameters with K_d values may be adequate in establishing the potential for PPCPs to reach groundwater. It is however, recommended that the mobility index be refined subject to the availability of soil property data from the study area.

4.2.1.3 Persistence

Once released into the environment, the potential for a PPCP residue to enter groundwater will depend on the time the compound remains in the environment, i.e. persistence or environmental fate. This persistence is influenced by numerous factors and both biotic and abiotic elimination pathways, such as biodegradation, hydrolysis and photodegradation (Boxall et al., 2004; Guillén et al., 2012; U.S. Environmental Protection Agency, 2009). Thus, the potential for each PPCP residue to remain in the environment and migrate to groundwater was assessed based on the degradation half-life (DT_{50}) of each compound, which measures the time required for 50% dissipation of the initial concentration (Beulke and Brown, 2001). In the third stage of the exposure assessment, the persistence index (P), was calculated using the degradation half-lives in both soil and water compartments, as persistence can be controlled by the degradation rate constant in each medium (Mackay and Webster, 2006) (Equation 4.3). It was assumed that degradation follows first-order kinetics, and the potential values for this index range from 0 to 1.

$$P = e^{-\frac{ln2}{DT50w*t}} * e^{-\frac{ln2}{DT50s*t}} \qquad (4.3)$$

Where P = the persistence index, DT_{50w} = half-life for a PPCP residue in an aqueous degradation study (days), and DT_{50s} = the half-life for a PPCP residue in a soil degradation study (days), and t = groundwater residence time (days).

As a conservative approach, we selected the highest water and soil degradation half-live values, where multiple values for the same parameter have been reported in either a hydrolysis, water or soil degradation study. It is worthy to note that the degradation half-lives of PPCPs are sometimes

not available, particularly for multimedia systems (e.g. soil and sediment/water systems), and for different degradation processes (e.g. hydrolysis and surface photolysis). However, in the absence of experimentally derived half-life values, one or a combination of estimation approaches can be used to predict the degradation rate of a compound in the environment. Missing biodegradation data of target PPCPs were estimated using various estimation software, including the USEPA PBT profiler (http://www.pbtprofiler.net/) and EPI suite Biowin software, which estimate the environmental fate of a molecule using its physico-chemical properties (US Environmental Protection Agency, 2016). The use of predictive modelling tools to assess chemicals without experimental data has been widely applied in various prioritization studies (Howard and Muir, 2011; Fàbrega et al., 2013; Ortiz De García et al., 2013).

Regarding residence time of contaminants in aqueous media, the TGD recommends a residence value of 40 days for use as the t-parameter for aquatic ecosystems (e.g. surface water) (European Commision, 2003); however, it is suggested that this value may be inappropriate and should be increased for groundwater, which has a relatively higher residence time than surface water (Sinclair et al., 2006). Groundwater residence times are important parameters in contamination and risk assessments (Kralik, 2015), as knowledge of groundwater residence times, particularly in the upper reaches of the aquifer improves our understanding of the long-term behaviour of groundwater systems in response to the influx of man-made pollutants (Kunkel & Wendland, 1997). Therefore, applying a higher t-value to estimate persistence is clearly more appropriate for more realistic estimates. Hence, we selected a t-value of 101days, which represents the annual average overall residence time from a study where groundwater residence time was estimated in ten hydrological stations in Wudinge River Basin, China (Zhu et al., 2010).

Calculating exposure index. In the final stage of the exposure assessment, the exposure index was calculated using the three previously characterized parameters of exposure - usage, mobility and persistence, to obtain a single index of exposure (E) using Equation 4.4 E is a unitless value

that allows a PPCP to be ranked according to its potential to enter source water relative to other PPCPs occurring within the specified system of interest.

$$E = A * F * P \quad (4.4)$$

Where E = the PPCP exposure index; A = PPCP amount index, F = mobility index, P = persistence index.

4.2.2 Estimating effects

Human health effect of PPCPs was characterized by evaluating their potential to cause long term adverse effects following chronic low-level exposure to PPCP residues in drinking water. The toxicological properties of PPCPs were defined using ADIs, which are considered the most relevant toxicological end point for drinking water safety as they measure the maximum amount of a chemical that can be ingested daily over a life time with no appreciable health risk (Sinclair et al., 2006).

4.2.2.1 Development of ADIs

In the present analysis, ADIs for selected APIs were estimated (Table 4.1) using the approach developed by Cunningham et al. (2009), which calculates ADIs (Equation 4. 5) from the lowest recommended total daily dose. Unlike the single dose approach (e.g. Schwab et al., 2005), the Cunningham et al. approach accounts for cases where multiple doses are required during a 24 hour regimen to elicit the desired pharmacological effect. The point of departure (POD) for determining the ADIs involved the use of either the lowest daily therapeutic dose, the lowest observed effect level (LOEL) derived from pre-clinical toxicology studies or the no observed effect level (NOEL). In some instances, microbial activity studies were used for antibiotic ADIs to account for risks associated with antibiotic resistance, an approach reported to be more conservative compared to when an ADI was derived from a toxicological endpoint (Cunningham et al., 2009).

The use of uncertainty factors has evolved over the years, where they were first introduced to account for inter and intra-species variability (Dourson et al., 1997). Appropriate uncertainty factors (UFs) were selected based upon extrapolation uncertainties that include: LOEL to NOEL (UF1); duration of exposure during toxicological studies (UF2); interspecies variability (UF3); intra-individual susceptibility (UF4), and a general data quality factor (UF5). In this study, the values selected for the uncertainty factors used the considerations described by Schwab et al. (2005).

$$ADI\ (\mu g/kg/day) = \frac{1000 * POD\ ((mg/kg)/day)}{UF1 * UF2 * UF3 * UF4 * UF5} \qquad (4.5)$$

For PCPs, ADIs were retrieved from authoritative and comprehensive chemical information databases. When ADIs were not available, they were calculated by extrapolating the lowest no observed adverse effect level (NOAEL) identified during mammalian toxicity studies and applying a 100-fold safety factor that accounts for inter-species and inter-individual variation. The uncertainty data from Schwab et al. (2005) is appropriate to use in Nigeria as it is based on scientifically acceptable methodology for the establishment of a health-based limit for APIs and are similar to those used by regulatory bodies such as the United States Food and Drug Administration (USFDA) to evaluate the safety of pharmaceuticals (US FDA, 2005). The UF4 accounts for the variability in sensitivity among members of the human population; this means that the variability in sensitivity to chemicals which may occur as a result of race, disease burden, pregnancy, age (children and the elderly) are accounted for under UF4.

4.2 3 Risk characterisation and Ranking

Risk characterisation represents the final phase in the prioritisation process, and a risk index (RI) is derived by comparing the PPCP exposure index with ADIs using Equation 4.6. A high-risk index

value in this context does not infer a greater source of risk but represents a higher relative priority for future groundwater monitoring.

$$RI = \frac{E}{ADI} \quad (4.6)$$

where RI= PPCP risk index; E= exposure index; ADI=acceptable daily intake (mg $kg^{-1}day^{-1}$)

4.3 Sources of data.

Data relevant to exposure and effect characterization including pharmacological and toxicological data (including non-clinical and clinical data on acute, chronic, developmental, reproductive, mutagenic and carcinogenic endpoints) for individual compounds were obtained from various authoritative sources such as the European Medicines Agency, comprehensive chemical information databases (e.g. Hazardous Substances Databank, MSDSonline, ChemSpider, PubChem, DrugBank; Toxnet, and ChemIDplus), reference handbooks about drugs and medicines (e.g. Martindale drug reference), relevant scientific peer reviewed literature and product monographs. Pesticides Properties Database (PPDB) provided information on the physicochemical properties of pesticides including DT50 values in both soil and water, which are a measure of pesticide stability and persistence in the environment. In the absence of experimental data, USEPA's EPISUITE software package provided estimates of environmental fate data such as partition coefficients (e.g. K_{ow} values), which are useful in predicting the distribution of chemicals between various environmental media such as soil, water, and air. The US PBT profiler provided estimates of DT50 values for individual compounds. The PBT profiler was designed to predict the persistence, bioaccumulation and aquatic toxicity potentials of chemicals in the absence of experimental data. Only data determined to be of high quality were

included and where multiple values have been reported for the same parameter, the most conservative value was used during prioritisation.

We also filled data gaps by adapting the ‘read across’ approach, which allows the use of hazard information from a structurally-similar compound to predict the toxicity behaviour of a compound with limited toxicity data. For example, in establishing ADIs for APIs, the hazard information for artemisinin (an antimalarial agent) was used to predict the toxicity profile of another antimalaria drug, artemether, which is a chemical derivative. The use of read-across method as an estimation tool to inform prioritisation and risk assessment has been previously reported (U.S. Environmental Protection Agency, 2009; Lalone et al., 2014; Huggett et al., 2010; Zanto et al., 2011).

Table 4. 1 Parameters for estimation of ADIs for APIs, critical effects and basis for POD

Compound	POD mg/kg/day	UF1	UF2	UF3	UF4	UF5	ADI mg/kg/day	Critical effect and basis for POD	Ref
Acetaminophen	27.8	3	3	1	10	3	0.10	Increased serum liver enzymes (ALT) in humans (LOAEL, POD is based on dosing of 1950mg/day) (Minnesota Department of Health (MDH), 2015)	6
Ciprofloxacin	NA	NA	NA	NA	NA	NA	0.0016	Sensitivity of human intestinal microflora. ADI of 1.6mcg/kg/day is based on minimum inhibitory concentration (MIC) values for ciprofloxacin (lowest MIC_{50} =0.0016mcg/ml) human intestinal flora following EMEA methodology	3
Ibuprofen	11.4	3	1	1	10	3	0.13	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 800mg, or 11.4 mg/kg in a 70-kg adult; (200mg taken four times/day for pain relief)	1
Metamizole sodium (Dipyrone)	14.3	3	1	1	10	3	0.16	Therapeutic dose. POD is the lowest recommended total daily dose in adult of 1000mg, or 14.3 mg/kg in a 70-kg adult; (500mg taken twice per day for the relief of moderate to acute pain)	1
Sulfamethoxazole	25	1	1	10	10	2	0.13	Animal Study NOEL. POD is based on NOEL for thyroid tumors in rats that may have no relevance in humans. POD is the 25mg/kg/day dose of the rat studies	2
Ampicillin	14.3	3	3	1	10	3	0.053	Therapeutic effect. POD is lowest recommended total daily dose in adult of 1000mg, or 14.3mg/kg in a 70-kg adult; (250mg taken four time per day for the treatment of urinary tract infection)	1
Tetracycline	NA	NA	NA	NA	NA	NA	0.03	Sensitivity of human intestinal microflora. ADI of 30mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal micro flora	4
Trimethoprim	NA	NA	NA	NA	NA	NA	0.0042	Sensitivity of human intestinal microflora. ADI of 4.2 mcg/kg/day was established by EMEA based on the in vitro minimum inhibitory concentration (MIC) of the most sensitive species in a study of trimethoprim activity against human gut flora.	5
Cloxacillin	14.3	3	3	1	10	3	0.053	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 1000mg, or 14.3 mg/kg in a 70-kg adult; (250mg taken four times per day for the treatment of bacterial infections)	1
Triprolidine	0.1	3	1	1	10	1	0.033	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 10mg, or 0.1mg/kg in a 70-kg adult; (2.5mg taken four times per day for the treatment of coughs and common cold)	1

Table 4.1 (Continued)

Compound	POD mg/kg/day	UF1	UF2	UF3	UF4	UF5	ADI mg/kg/day	Critical effect and basis for POD	Ref
Guaifenesin	11.4	3	3	1	10	3	0.042	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 800mg, or 11.4mg/kg in a 70-kg adult; (200mg taken 4 time a day for use as expectorant for productive cough	1
Dextromethorphan	0.9	3	1	1	10	1	0.030	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 60mg, or 0.9mg/kg in a 70-kg adult; (10mg taken every four hours for the relief of non-productive cough	1
Diphenhydramine	1.1	3	1	1	10	2	0.018	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 75mg, or 1.1mg/kg in a 70-kg adult; (25mg taken 3 to 4 times daily for the treatment of coughs and common cold in adult)	1
Pseudoephedrine	3.4	3	1	1	10	2	0.057	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 240mg, or 3.4mg/kg in a 70-kg adult; (60mg taken every 4 to 6 hours for the symptomatic relief of nasal congestion in adult	1
Chloroquine phosphate	10	3	3	1	10	1	0.11	Therapeutic effect. POD is recommended total daily dose in adults of 10mg/kg/day for the treatment of malaria caused by *P. vivax P. ovale* and *P. malariae*	1
Quinine sulphate	25.7	3	3	1	10	1	0.29	Therapeutic effect. POD is the lowest recommended total daily dose in adults of 1800mg or 25.7mg/kg in a 70-kg adult; (600mg taken three times per day for malaria treatment)	1
Lumefantrine	20.6	3	3	1	10	3	0.076	Therapeutic effect. POD is lowest recommended total daily dose in adults of 1440mg, or 20.6 mg/kg in a 70-kg adult; (480mg taken in three doses in the first 24 hours for the treatment of uncomplicated falciparum malaria in adults)	1
Artemether	3.4	3	3	1	10	3	0.013	Therapeutic effect. POD is the lowest recommended total daily dose in adult of 240mg or 3.4 mg/kg in 70-kg adult; (80mg taken in three doses in the first 24 hours for the treatment of uncomplicated falciparum malaria in adults)	1
Artesunate	4	3	3	1	10	1	0.044	Therapeutic effect. POD is the lowest recommended total daily dose in adult of 4mg/kg for treatment of malaria	1

1:) Martindale (2011); 2 Schwab et al., 2005; 3) EMEA, 1998; 4) WHO, 1998; 5) EMEA, 1997; 6) Minnesota Department of Health, 2015

4.4 Priority list for PPCPs in southern Nigeria

To illustrate the proposed approach, a priority list of PPCPs was developed for southern Nigeria. Data on the amounts of APIs and PCP active ingredients were obtained from 2016 survey data (Chapter 3), which provided PPCP annual usage per capita per year. To obtain a regional estimate of use, a total annual mass consumed was extrapolated to reflect use by approximately 32 million inhabitants of southern Nigeria (Table 4.2)

4.5 Results and Discussion

The risk-based prioritization approach described above ranked PPCPs according to their potential to enter groundwater following onsite wastewater treatment, using a combination of exposure and effects measures. The dataset used to illustrate this prioritization scheme contains 19 APIs and 22 PCP active ingredients. For the sake of simplicity, this study focused on community use data due to limited access to sales and hospital data. In addition, only parent compounds were considered as limited data exist regarding metabolites and transformation products for most products. The estimated annual usage mass (kg/yr.), ranged over three orders of magnitude for APIs (10^3kg/yr.(triprolidine) – 10^6kg/yr.(acetaminophen) (Table 4.2.) and over five orders of magnitude for PCP AIs (10^3kg/yr. (cyfluthrin) and 10^8kg/yr. (LAS) (Table 4.3). The results indicate that 73.7% (n=14) of APIs (Table 4. 2) and 40.9% (n=9) of PCP AIs (Table 4.3) evaluated had RI ≥ 0.01; this indicates that these compounds have the greatest potential to be available in groundwater and are therefore high priority compounds for future groundwater monitoring in southern Nigeria.

Among the top 14 ranked APIs (ciprofloxacin, trimethoprim, ampicillin, tetracycline, sulfamethoxazole, cloxacillin, acetaminophen, pseudoephedrine, metamizole, guaifenesin, diphenhydramine, artesunate, artemether and dextromethorphan), the majority are antibiotics. Interestingly, the results of the current prioritization scheme agreed with the findings of previous prioritization studies from other countries. In a recent review of global prioritization approaches, Burns et al. (2018), identified 76 prioritization exercises covering 24 countries,

and found antibiotics and analgesics to be the dominant therapeutic classes, with four top ranking APIs in this study (ciprofloxacin, sulfamethoxazole, trimethoprim and paracetamol) being among the pharmaceuticals most commonly identified as priority compounds. Ciprofloxacin, the compound with the highest RI in this study, appeared among the top 20 compounds ranked to be potentially toxic for both human and aquatic species in a study that prioritized 200 compounds across 12 toxicity endpoints (Dong et al., 2013). In Switzerland, ciprofloxacin, alongside sulfamethoxazole and paracetamol has been included in a priority list for environmental risk assessment (Perazzolo et al., 2010). In a recent risk-based prioritization study in the UK, ciprofloxacin had a risk score >1 (Guo et al., 2016), and has recently been added to the watch list of the Water Framework Directive (Carvalho et al., 2015).

Although the evaluation in this study was limited to parent compounds, it needs to be said that the metabolite and transformation by-products of sulfamethoxazole (sulfamethoxazole hydroxylamine), and acetaminophen (I,4-benzoquinone), for which both parent compounds ranked high in the current study were considered to have high toxicity levels of risk based on preliminary rankings for the most consumed PPCPs in Spain (Ortiz De García et al., 2013). The occurrence of ciprofloxacin, sulfamethoxazole, trimethoprim and paracetamol has been reported in groundwater impacted by septic systems in the United States (Hinkle et al., 2005; Godfrey et al., 2007; Phillips et al., 2015; Verstraeten et al., 2005; Schaider et al., 2014; 2016; Katz et al., 2010; Dougherty et al., 2010). The environmental occurrence of antibiotics has raised concerns about the evolution and dissemination of antibiotic resistance in bacteria (Bengtsson-Palme & Larsson, 2016). The proliferation of antibiotic resistance subsequently renders antibiotic treatment ineffective, in both humans and animals thereby compromising public health (Santos et al., 2010). Four high ranking antibiotics in this study (ciprofloxacin, ampicillin, tetracycline and trimethoprim), have been associated with the occurrence of resistant strains of bacteria in water and sediment samples from Canada (Maal-Bared et al., 2013).

Table 4. 2 Priority list of APIs for groundwater monitoring in unsewered communities in southern Nigeria

API	CAS No.	Functions/uses	API usage (U) (Kg yr^{-1})	Sorption K_d ($cm^{-3}g^{-1}$)	Persistence water (DT50w) (days)	Persistence Soil (DT50s) (days)	Mobility Index	API ADI (mg kg^{-1} d^{-1})	Risk Index
Ciprofloxacin	85721-33-1	Antibacterial	90100.00	0.04	696	2310	0.759	0.0016	179.4
Trimethoprim	738-70-5	Antibacterial	22440.00	0.14	30.4	74	0.492	0.0042	18.4
Acetaminophen	103-90-2	Analgesics	3150780.00	0.06	4.28	2.1	0.692	0.10	6.885
Tetracycline	60-54-8	Antibacterial	53380.00	0.002	2.61	86.6	0.984	0.030	5.71
Ampicillin	69-53-4	Antibacterial	610640.00	0.31	27	75	0.299	0.053	3.93
Sulfamethoxazole	723-46-6	Antibacterial	111860.00	0.13	273	10	0.502	0.13	3.02
Guaifenesin	93-14-1	Expectorant	332520.00	0.34	15	30	0.284	0.042	1.47
Pseudoephedrine	90-82-4	Nasal Decongestant	39780.00	0.13	15	30.1	0.502	0.057	0.99
Metamizole	68-89-3	Analgesics	301920.00	0.6	1.16	75	0.182	0.16	0.71
Cloxacillin	61-72-3	Antibacterial	379100.00	2.57	60	120	0.049	0.053	0.59
Diphenhydramine	58-73-1	Antihistamines	87040.00	11.2	14	1000	0.012	0.018	0.05
Artemether	71963-77-4	Antimalarial	105400.00	18.2	60	4.22	0.0070	0.13	0.048
Artesunate	88495-63-0	Antimalarial	13260.00	8.17	38	75	0.016	0.044	0.021
Quinine sulphate	130-95-0	Antimalarial	86700.00	15.4	180	360	0.0090	0.29	0.0080
Ibuprofen	15687-27-1	Anti-inflammatory	27880.00	41.4	32	34.3	0.0030	0.13	0.0060
Dextromethorphan	125-71-3	Cough suppressants	32980.00	20.8	60	120	0.0060	0.030	0.0050
Chloroquine Phosphate	50-63-5	Antimalarial	14960.00	141.7	60	120	0.0010	0.11	0.0010
Triprolidine	486-12-4	Nasal Decongestant	1360.00	37.7	60	120	0.0040	0.0030	0.00020
Lumefantrine	82186-77-4	Antimalarial	105400.00	143360.7	60	120	9.3E-07	0.687	1.07E-06

API -active pharmaceutical ingredient; DT_{50W} – degradation half-life in water; DT_{50s} – degradation half-life in soil; ADI – acceptable daily intake; K_d – soil adsorption coefficient

Table 4. 3 Priority list of PCPs for groundwater monitoring in unsewered communities in southern Nigeria

PCP	Cas No.	Functions /Uses	PCP usage (U) (Kg yr^{-1})	Sorption K_d ($cm^{-3}g^{-1}$)	Persistence water ($DT_{50\ w}$) (days)	Persistence Soil (DT50s) (days)	PCP ADI (mg kg^{-1} d^{-1})	Mobility Index	Risk Index
Dichlorvos (DDVP)	62-73-7	Organophosphate insecticide	29408000	1	4.7	2	0.0005	0.12	5.69
Sodium carbonate	7542-12-3	Water softener	29536000	0.00001	15	30	1.79	0.1	0.11
SLES	9004-82-4	Surfactant	84384000	1.2	75	38	1	0.01	0.06
Ammonium thioglycolate	5421-46-5	Perm salt	2432000	0.003	15	30	0.4	0.1	0.04
Cresol	108-39-4	Antibacterial agent	33728000	3	180	360	0.3	0.04	0.03
Cetrimide	1119-97-7	Antiseptic	1888000	2.3	60	108	0.025	0.06	0.03
Alcohol ethoxylate	68439-46-3	Surfactant	42528000	178.3	2.5	5	0.01	0.001	0.02
Chlorhexidine	55-56-1	Disinfectant	4992000	29.84	180	360	0.01	0.004	0.01
Hydroquinone	123-31-9	Skin lightening agent	800000	0.77	0.833	30	0.1	0.15	0.01
LAS	67774-74-7	Surfactant	151168000	67.8	2	26	0.5	0.002	0.004
Glycerine	56-81-5	Moisturizer	8320000	0.003	8.7	17	34.43	0.1	0.002
Triclosan	3380-34-5	Antibacterial	537600	368.2	60	187	0.0019	0.0004	0.001
Chloroxylenol	80-04-0	Antiseptic/disinfectant	33728000	28	38	75	1.8	0.005	0.001
Transfluthrin	118712-89-3	Pyrethroid insecticide	96000	151.6	15	30	0.003	0.001	0.0002
Imiprothrin	72963-72-5	Pyrethroid insecticide	9600	8.04	58.6	5	0.05	0.02	2.1E-05
Prallethrin	23031-36-9	Pyrethroid insecticide	9600	69.14	38	75	0.02	0.002	6.1E-06
Tetramethrin	7696-12-0	Pyrethroid insecticide	22400	28.5	365	11	0.2	0.005	3.5E-06
Triclocarban	101-20-2	Antimicrobial	576000	1002.4	60	108	0.25	0.0001	2.0E-06
d-phenothrin	26002-80-2	Pyrethroid insecticide	480000	3600	173	60	0.07	3.7E-05	1.7E-06
Permethrin	52645-53-1	Pyrethroid insecticide	64000	2000	23	42	0.05	6.7E-05	5.6-E-07
Cyfluthrin	68359-37-5	Pyrethroid insecticide	3200	2478.6	215	33	0.003	5.4E-05	3.8E-07
Deltamethrin	52918-63-5	Pyrethroid insecticide	6400	204800	4.7	2	0.01	6.5E-07	2.7E-09

LAS - Linear alkylbenzene sulfonate; SLES - Sodium Lauryl Ether Sulphate; DDVP - 2,2-dichlorovinyl dimethyl phosphate; API -active pharmaceutical ingredient; DT_{50W} – degradation half-life in water; DT_{50s} – degradation half-life in soil; ADI – acceptable daily intake; K_d – soil adsorption coefficient

In the south western region of Nigeria, Oluyege et al. (2009) reported the prevalence in groundwater of organisms exhibiting multiple antibiotic resistance to tetracycline, a top ranking antibiotic this study.

In terms of usage volume, paracetamol is the top used compound in this study, and its top use has been reported in Iraq (Al-Khazrajy & Boxall, 2016) and Sweden (Dong et al., 2013). Paracetamol has been detected in groundwater recharged by septic systems in the Unites States, alongside other compounds considered in this study, including ciprofloxacin, sulfamethoxazole, trimethoprim, ibuprofen and diphenhydramine (Hinkle et al., 2005; Verstraeten et al., 2005). Although it has been reported that exposure to APIs through drinking water consumption poses no appreciable risks to humans (Schwab et al., 2005), there are concerns about the likelihood that multiple chemical exposures could lead to unexpected adverse effects on human health due to the potential for mixture toxicity (Wilkinson et al., 2000). Two antimalarial agents, artesunate and artemether were among the high-ranking compounds in this study but no previous prioritization study has ranked antimalarial agents as compounds of concern. Ibuprofen showed low risk index score and had a low ranking in this study. This deviates from findings which show ibuprofen as one of the five pharmaceuticals most commonly identified as priority compounds in several prioritization studies (Burns et al., 2018). It is therefore not surprising that Ibuprofen has been detected in groundwater affected by septic systems in other regions, including the United States (Del Rosario et al., 2014; Hinkle et al., 2005; Verstraeten et al., 2005) and Canada (Carrara et al., 2008). The relatively low risk index value of ibuprofen (RI = 0.0002) may reflect its reported low annual usage relative to other analgesics consumed in the study area. This underscores the potential for regional differences in priority compounds, which according to Burns et al. (2018) suggest that exposure and risks are also region specific, and limits the generalization of prioritization outcomes (Dong et al., 2013). As previously discussed, it has been recognized that prioritization results from one geographical region may not be adaptable to another location due to differences in usage patterns resulting from such drivers as national marketing

authorization approaches, pharmaceutical costs, prescribing practices, disease burden, wastewater treatment and connectivity and consumption trends in different populations (Burns et al. 2018; Ortiz De García et al., 2013).

In the case of PCP AIs, the most relevant in terms of their potential to enter groundwater include dichlorvos (organophosphate insecticide), sodium carbonate (water softener), ammonium thioglycolate (perm salt), cetrimide (antiseptic), cresol (antibacterial agent), chlorhexidine (disinfectant) and all surfactants considered. Dichlorvos, the compound with the highest RI in this study, is highly soluble in water (18000mg/L) and has a low soil adsorption coefficient (log K_{oc} = 1.4), which indicates its predominance in the aqueous phase and a great potential for mobility in soils (Mccall et al., 1980). Its top RI value in this study reflects its high usage, high mobility index (ranked 5) and its generally low ADI (Table 4. 3). The occurrence of dichlorvos has been reported in surface water samples from China (Gao et al., 2009) and Turkey (Tuncel et al., 2008) and in groundwater samples from Northern Vietnam (Lamers et al., 2011). Other high ranking compounds in this study, notably the biocides (disinfectants and surfactants), are recognized as resistant-driving chemicals, with the potential to select for resistant genes in the environment (European Commission, 2009). However, among the 140 biocides currently in use in the EU, only about 29 biocides are routinely monitored. Only about 15% of the compounds approved as biocides in the EU have monitoring data limited to surface water. Groundwater monitoring data for biocides are almost totally absent (Pohl et al., 2015). Limited access to biocide monitoring data results in inadequate information about their environmental occurrence, which is critical for determining the degree to which they may be of ecological concern (Pohl et al., 2015). Interesting, all pyrethroid insecticides (Table 4.3) ranked within the bottom 6 in this study. However, based on the NORMAN prioritization scheme for surface water monitoring deltamethrin (pyrethroid insecticide) and triclosan (disinfectant) require control/mitigation measures (Pohl et al., 2015). NORMAN is a Network of reference laboratories, research centres and related organizations for monitoring of emerging environmental substances. The low RI values for pyrethroid insecticides is not

surprising as they are volatile and are therefore unlikely to reach groundwater via the assessed pathway. The confirmed environmental presence of most of the high-ranking compounds in this study provides to a degree of validation for the prioritization approach using survey data in the absence of available countrywide usage data. Therefore, the prioritized list represents a useful starting point for future groundwater monitoring campaigns in the study area.

It is important to highlight that the present prioritization scheme was not designed to estimate environmental concentrations of PPCPs but serves as a mere ranking tool, and as such, a high-ranking index does not infer that the substance poses a greater source of risk to the general population than other PPCPs listed but represents a higher relative priority for future groundwater monitoring than PPCP residues with a lower risk index ranking within the specified geographical area. The simplicity of this approach makes it adaptable to different geographical areas, particularly developing countries, where there is often a huge reliance on septic systems (Kookana et al., 2014), where source water is often consumed without treatment and national usage and consumption data are unavailable. To our knowledge, PPCPs have not been previously prioritized in groundwater affected by onsite wastewater treatment systems in low- to middle-income countries, and through this exercise, a list of chemicals of concern to inform future groundwater monitoring programs has been compiled.

4.5.1 Strengths and limitations of the method

The current prioritization scheme is relatively simple, quick and can be easily applied to many compounds, to facilitate the objective screening of compounds with higher relative priority for groundwater monitoring and subsequent risk assessment. In addition, by excluding the 'treatability in water utilities' criterion from consideration, this present scheme can be applied in many developing countries where there is often a lack of water treatment facilities. Furthermore, the prioritization scheme considered some APIs (e.g. antimalarial agents), which hitherto have not been previously examined; this inclusion compensates for the so-called

‘Mathew effect’ (or ‘bandwagon effect’), which is a term describing the continual consideration of previously identified compounds from prior studies and the neglect of other potential environmental stressors (Daughton, 2014). This prioritization scheme has also considered a different pharmaceutical source (onsite wastewater treatment systems vs wastewater treatment plant (WWTP)) and a different reservoir of concern (groundwater systems vs surface water), which until now, have not been the focus of any prioritization study. In many low- to middle-income countries, sewage treatment is predominantly by septic systems, and groundwater is often the primary source of water supply. Not considering this pathway and reservoir overlooks potential risks from exposure to wastewater contaminants in these regions, despite considerable evidence to suggest that these risks may be present. Therefore, this prioritization scheme has addressed a research need previously highlighted by Burns et al. (2018), and improved prioritization efforts by accounting for an understudied environmental pathway and compartment by considering a PPCP source other than municipal WWTPs.

However, the prioritization scheme has a few limitations. Due to the absence of a countrywide statistical data on API use and the difficulty associated with obtaining hospital-based data partly due to the issues of confidentiality, the API dataset considered in this study was based on 2016 household usage survey data of 350 respondents, a source which may likely provide a less accurate estimation of use in the general population. Hence, although the use of surveys has been suggested as one of the ways of estimating API usage within a country (Kostich et al., 2010), this method has not been widely applied and therefore its accuracy is uncertain and can only be validated against monitoring data. Another constraint is the uncertainty about the accuracy of model estimates which were used as substitutes for non-existing experimental data (such as degradation rates) for several compounds in this study. For this reason, it has been recommended that in such cases, estimated values be used only on a screening level (Aronson et al., 2006). Finally, only parent compounds were considered. However, APIs can be metabolized after use, or if excreted intact, can degrade in the environmental media resulting in metabolites and degradation products, which in some cases

could be more potent than the parent compounds (Boxall et al., 2004). Hence, future prioritization exercises should consider transformation products as relevant data on these compounds become more readily available.

4.6 Conclusion

An approach has been developed to determine the relative priority of PPCP residues that may pose a risk to human health in Nigeria. This method is based on the potential for indirect exposure of the general population to PPCP residues in drinking water supplies that may be affected by onsite wastewater treatment systems. PPCP usage data has been used together with information on physicochemical properties and toxicological profile of PPCPs to generate a risk index, which ranks compounds according to their relative potential to reach groundwater. Fourteen APIs including (antibiotics, analgesics, antimalarial agents, antihistamines, suppressants and decongestants) and nine PCP active ingredients including (organophosphate insecticides, biocides and surfactants) have been identified as high priority substances. The study indicates that antibiotics, analgesics, and biocides appear to be the most important classes of chemicals in terms of their potential to be available in groundwater. Risk to humans through drinking water consumption may be low when water is processed before use but the removal of PPCP residues by this method was neglected due to the nonexistence of water treatment utilities in Nigeria. Future groundwater monitoring campaigns guided by the prioritized list is recommended to ascertain the presence of these compounds in groundwater and characterize the nature of any potential risk. While the dataset of 41 compounds is by no means an exhaustive list of APIs and chemical constituents in consumer products, this simple prioritization strategy could be widely applied to derive a priority list of contaminants from a much larger dataset for groundwater monitoring in septic system reliant areas.

Chapter 5

Occurrence of active pharmaceutical ingredients and dichlorvos (household insecticide) in groundwater (drinking water) in southern Nigeria

5.1 Introduction

Domestic wastewater is recognized as a significant source of global environmental pollution, and in Nigeria and many other developing countries, it is an important source of contamination to drinking water supplies, particularly groundwater resources. In septic system reliant areas (e.g. unsewered communities), it is estimated that several trillion liters of wastewater may be released from septic systems to the subsurface annually (Scandura & Sobsey, 1997) and because septic systems do not eliminate all contaminants associated with residential wastewater (Berto et al., 2009), onsite systems become hotspots of a wide range of wastewater borne contaminants (particularly unconventional pollutants such as PPCPs) in the environment (Yang et al., 2016), notably unprotected aquifers, which are the ultimate sinks of contaminants from onsite wastewater disposal (Verstraeten et al., 2005).

About three in four Nigerian households treat wastewater by septic systems (Adesogan, 2013) due to a lack of centralized sewerage system (Gandy, 2006), and more than 80% of households rely on groundwater as the major source of drinking water (Pavelic et al., 2012), due to non-existent or inadequate public or municipal water supply systems (Adekunle et al., 2007). Groundwater may be extracted at various depths, ranging from less than 3 meters for shallow wells (hand dug wells) to 30 meters, sometimes more for deep wells (borehole systems) (Adelana et al., 2008), and these wells are often in close proximity (<15 m) to septic system seepage pits.

Many factors can facilitate the pollution risk of local water supplies by septic systems. Such factors as well depth, setback distance (i.e. location of the well relative to the location of nearby septic system seepage pit), septic system density (referring to the number of septic systems

per unit of land area) and hydrogeological conditions (e.g. distribution and movement of groundwater in the soil), have been found to contribute to the vulnerability of groundwater to contaminants from septic systems (Bremer and Harter, 2012; Nielsen, 2016), and this may be potentially the case for Nigeria. The growing Nigerian population, which in recent years, has resulted in an increase in urban sprawl and the concomitant development of large residential housing units potentially increase ground water pollution risk of onsite wastewater treatment as these newly developed housing units also rely on septic systems for sewage disposal. In 2016, nearly half (48.6%) of the Nigerian population lived in urban areas (Trading Economics, 2019) and the consequence of rapid urban development in unsewered communities is that the number of septic systems increases significantly. The average plot size in many Nigerian urban areas is approximately 450 m^2 which translates to a septic system density of about 6 to 8 septic systems per acre of land. Such a density of septic systems has been recognized as a significant threat to the underlying aquifer, adjacent domestic water wells and nearby surface water (Bremer and Harter, 2012; Carroll et al., 2004).

Furthermore, studies investigating aquifer characteristics reveal that in many parts of Nigeria, shallow unconfined aquifer is characterized by porous sandy soils and gravelly units, with little clay intercalations and low levels of organic matter (Ehirim and Nwankwo, 2010; Onwuka et al., 2013; Ibe et al., 1999; Ehirim and Ofor, 2011). These features, which allow relatively fast movement of groundwater and limited breakdown of contaminants, may lead to poorly attenuated septic system discharges (Barber et al., 1988) and are likely to result in degraded groundwater quality and unsafe groundwater resources in Nigeria. These issues underscore the need to assess the potential effect of septic systems on ground water quality in southern Nigeria, with focus on unconventional pollutants such as PPCPs, some of which are known to be poorly removed during anaerobic septic tank treatment (Conn et al., 2010).

A number of studies have explored the potential for PPCPs (and their degradation products) to migrate from septic systems to downgradient groundwater and adjacent drinking water wells (Verstraeten et al., 2005; Swartz et al., 2006; Carrara et al., 2008; Conn et al., 2010; Lowe

et al., 2009; Katz et al., 2009; Kolpin et al., 2002; Schaider et al., 2011; 2013; 2014; 2016). In particular, the extensive research undertaken by Schaider and colleagues has demonstrated a consistent trend in the contamination of drinking water supply wells in Cape Cod, Massachusetts by septic system leachates. Findings from their study of EOCs in drinking water wells in Cape Cod show the presence of a variety of EOCs (including pharmaceuticals, per-fluorinated chemicals, flame retardants, hormones, skin care products, insect repellent, plastic additives and artificial sweetener) in both private and public drinking water wells impacted by septic systems (Schaider et al., 2011; 2014; 2016). In Nebraska, Verstraeten et al. (2005) evaluated the vulnerability of shallow domestic wells to leachates from septic systems and found increased detections (e.g. 13 out of 26 wells) and higher concentrations (up to 750 ng/L) of non-prescription drugs and antibiotics in relatively more shallow wells (about 6 m deep) and in wells closest to drain fields (about 8 m apart). Swartz et al. (2006) reported the transport of steroid estrogens, (estrone and estradiol), caffeine and its degradation product paraxanthine and nonyl-phenol (a surfactant metabolite) from septic tanks to groundwater receiving partially treated effluent in Cape Cod. In Ontario, Canada, Carrara et al. (2008) observed that over 80% of pharmaceutical compounds detected in septic effluent were found in groundwater samples at concentrations in the low ng/L to low µg/L range.

Most of the studies investigating PPCPs in the environment and the associated public health risk are focused mainly in Europe, United Kingdom and North America (aus der Beek et al., 2016). The lack of extensive research regarding environmental occurrence of PPCPs in many developing countries creates a significant knowledge gap in these regions, particularly the African region. There is currently only a few published studies in Africa on the occurrence of PPCPs in wastewater effluent and the aquatic media, largely surface waters (Inam et al., 2015; Agunbiade and Moodley, 2014; K'oreje et al., 2016; 2018; Manickum and John, 2014). Agunbiade and Moodley (2014) reported the occurrence of several antibiotics (chloramphenicol, ciprofloxacin, ampicillin, sulfamethoxazole, streptomycin, tetracycline and

nalidixic acid), antipyretics, beta-blockers and caffeine in wastewater treatment plant effluent and surface water in South Africa. Another South African study found steroid hormones (including estrone (E1), 17-β-estradiol (E2), estriol (E3), 17-α-ethinylestradiol (EE2), testosterone and progesterone) at concentrations ranging from 11 ng/L to 480 ng/L in sewage treatment plant effluent and adjacent surface water in Pietermaritzburg (Manickum & John, 2014). In two separate studies, a wide range of pharmaceutical compounds including antibiotics, antiretrovirals, analgesics, anti-inflammatory and psychiatric drugs have been reported in WWTP effluent, surface and groundwater in Kenya (K'oreje et al., 2018; 2016). Inam et al. (2015) reported the occurrence of bisphenol A (fire retardant), two antibiotics (chloramphenicol and erythromycin) and two antimicrobials (triclosan and triclocarban) in a freshwater ecosystem in the Niger Delta in Nigeria. No previous studies have been conducted in Nigeria to characterize PPCP occurrence in groundwater affected by septic systems.

As previously discussed (Chapter 1, Section 1.3) septic systems in Nigeria are not operated under performance-based standards and codes and there is currently no agency in Nigeria responsible for monitoring groundwater quality to determine its suitability for potable use (Adelana et al., 2008). Given that routine monitoring of wells to assess groundwater quality is lacking, it is therefore not clear whether drinking water supplies meet drinking water standards for both internationally regulated and unregulated contaminants. There is a growing concern about the suitability of domestic wells as sources of potable water in Nigeria (Adelana et al., 2008), as the evidence of groundwater pollution by conventional wastewater contaminants (such as fecal coliform) from septic systems continues to grow (Fubara-Manuel & Jumbo, 2014; Eze and Eze, 2015; Oluwasola et al.,2017; Farouq et al.,2018). This study was therefore conducted to 1) characterize the occurrence and concentrations of PPCPs in domestic water wells; 2) evaluate whether the occurrence of PPCPs in domestic water is correlated with factors that influence septic system impact on groundwater quality; 3) compare measured environmental concentrations (MEC) in this study with levels from septic system related water

quality studies reported elsewhere; and 4) provide a screening level database on the occurrence of pharmaceuticals in groundwater in southern Nigeria.

5.2 Materials and Methods

5.2.1 Study Area

The study area, which includes Port Harcourt metropolitan area and Enugu metropolitan area in the southern region of Nigeria (Fig.5.1), is representative of many urban and suburban settings in Nigeria. In Port Harcourt and Enugu metropolitan areas (here after PHMA and ENMA, respectively), there is a huge reliance on domestic water wells as the main source of potable water and wastewater is treated and disposed by septic systems.

PHMA is located along the Bonny River in the Niger Delta region of south-south geopolitical zone of Nigeria and comprises approximately 2 million inhabitants. The topography of PHMA is essentially flat, sloping gently towards the sea, with elevations not exceeding 20 m above the sea level (Nwankwoala and Ngah, 2014). An extensive freshwater bearing unconfined aquifer is exploited for domestic water supply and it is characterized by high yields and recharge capacities (Adelana et al., 2008). The aquifer is largely unconsolidated, consisting predominantly (>90%) of a geological sequence of highly permeable sands and gravels with limited shale and clay intercalations; the latter becoming more prominent seawards (Adelana et al., 2008). In the Niger Delta Region, water table is shallow, ranging from 3 to 15 m below ground level and well depths range from 10 to 800 m (Adelana et al., 2008).

ENMA is located at the foot of the Udi Plateau of the south east geopolitical zone of Nigeria and comprises approximately 717,291 inhabitants. The topography is mostly steep and often rocky, characterized by numerous escarpment landforms, often with incised valley and canyons (Odumodu and Mode, 2017). ENMA and many adjoining areas overlay the Enugu Shale Formation, which is characterized by dark gray shales and mudstones, with intercalations of sandstones and sandy shales (Omonona et al., 2014; Onwuka et al., 2004).

The unconfined fractured portion of the Enugu Shale Formation is generally discontinuous when intercepted by a fresh bedrock and constitutes the only aquifer (Enugu Shale aquifer) in the metropolis exploited for domestic water supply. Groundwater which is characterized by seasonally high water levels and well depths ranging from 3.5 to 12.5 meters is extracted using shallow hand-dug wells (Omonona et al., 2014).

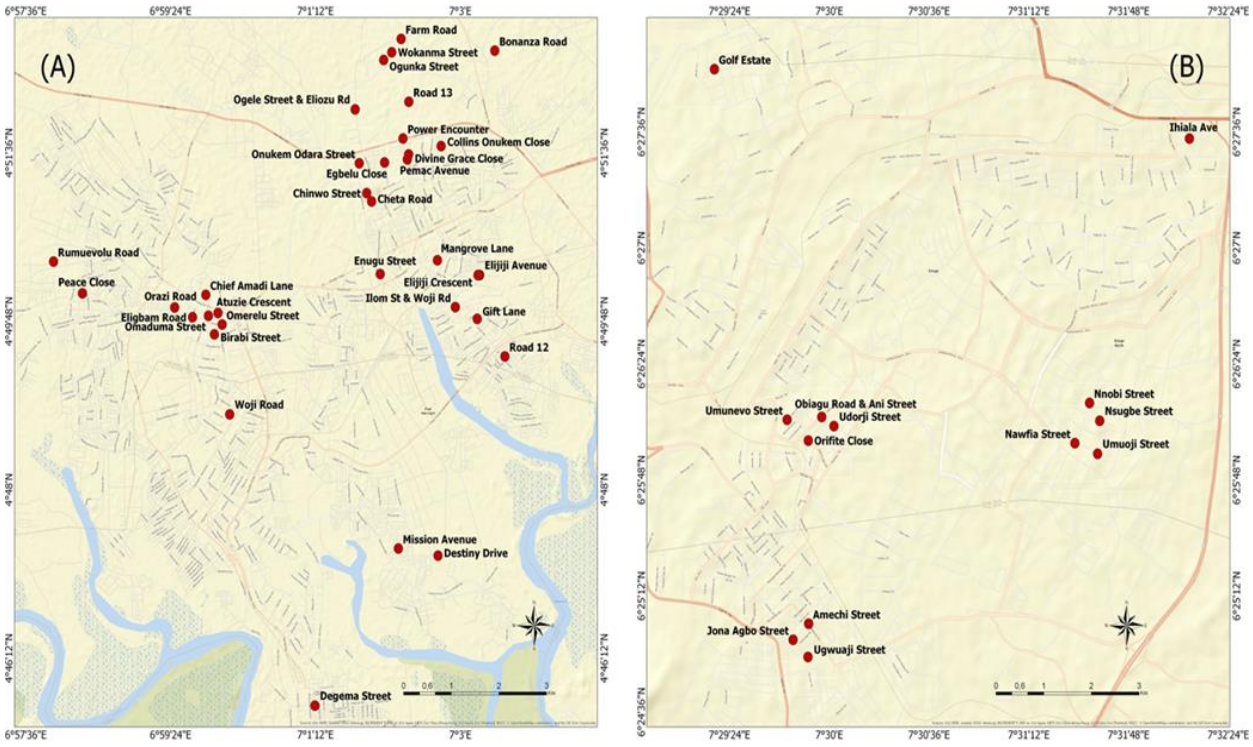


Figure 5. 1 Study area showing groundwater sampling locations

5.2.2 Site Selection and Sampling

Groundwater sites sampled during 2017 were selected in areas which rely on domestic water wells as a primary source of potable water. Domestic water wells downgradient of septic systems were prioritized for sampling as they would be more susceptible to contamination from septic effluent discharges. Most of the wells sampled were in close proximity (e.g. <15 m) to septic system soakaway pits and to adequately explore the impact of septic systems on groundwater, wells in locations in highly built up areas and are characterized by high spatial septic system density (e.g. 6-8 households per acre of land) were prioritized for sampling. The sampling network consisted of 53 wells across two metropolitan areas in southern Nigeria. Water samples were collected once from these wells and as such, temporal variability in PPCP occurrence cannot be established. Sampling followed the procedure described by Schaider et al. (2016); to minimize possible sample contamination, the field team avoided the use of products containing target analytes such as common non-prescription medications, insect repellents, and caffeinated beverages during sample collection. Thirty-seven samples were collected from spigots and kitchen taps in homes served by deep wells (about 30 m or more) and 16 samples were collected from shallow hand dug wells (15 m or less) using stainless steel bailers. To minimize contact time with the well casing and to provide a native water flush for the pumps, discharge lines were purged for approximately 5-10 minutes prior to sampling. To remove particulates and associated bacteria which could enhance analyte degradation (Burns et al., 2018), and to reduce matrix effects that could occur through direct injection during analysis (Boix et al., 2014), groundwater samples were passed through a primed 0.45 µm baked glass-fibre filter (Whatman Inc) in the field where possible, otherwise filtration was conducted in the laboratory. Although concerns have been raised about the potential for analyte loss during filtration to remove organic matter (Burns et al., 2018), Mompelat and coworkers (2013) through pharmaceutical filtration studies with 26 compounds of varying characteristics, concluded that such losses were insignificant (<5%).

Samples were collected in duplicates (as backup samples should there be breakage of primary samples during shipping) in pre-cleaned amber glass bottles and immediately chilled in the field using ice packs. Frozen samples were transported in iceboxes to the University of York (York, UK) Environmental Laboratory and stored at -18 ^{o}C until analysis, which was performed at the University of York Centre of Excellence in Mass Spectrometry (CoEMS).

5.2.3 Test Compounds

Target compounds comprising a suite of 61 APIs and 1 organophosphate insecticide (dichlorvos) (Table 5.1) were selected for analysis based on the following criteria: i) known or suspected usage ii) top ranking compounds in the priority list of PPCPs derived from the risk-based prioritization scheme developed in Chapter 4; iii) results from previous studies carried out in other countries documenting PPCP occurrence in groundwater impacted by septic systems; iv) potential for adverse human health effects (toxicity) and v) established analytical methodology (analytical consideration).

5.2.4 SPE Procedure

The SPE procedure was developed and optimized following published procedures (Bonansea et al., 2013; Peček et al., 2013; Ma et al., 2017). Dichlorvos was isolated from groundwater samples using Oasis HLB, 3 cc, 60 mg SPE cartridges (Waters, UK). The SPE cartridges were preconditioned using 3 mL of ethyl acetate, followed by 3 mL of Ultrapure water; then 100 mL of samples were passed through the SPE cartridge by employing a moderate vacuum using a 12-port Supelco Vacuum Manifold (Supelco Visiprep^{TM}, UK), at a flow rate of 10 mL min^{-1}. Next, SPE cartridges were air dried for 30 min under vacuum and the retained analytes were eluted with 2 mL of ethyl acetate. The eluates were collected with clean test tubes and evaporated to dryness under a gentle nitrogen stream in a DB 3A, TECHENE (UK) concentrator. The extract was reconstituted with 100 µL of hexane and then refrigerated at -20 ^{o}C prior to analysis by GC-MS.

Dichlorvos was purchased from Sigma-Aldrich, UK and was of > 98% purity. All solvents used for sample processing and analysis (ethyl acetate, hexane, methanol) were of HPLC grade.

5.2.5 Instrumental Analysis

Two separate analytical methods were used to determine the environmental extent of target compounds in groundwater samples. APIs were analyzed by high performance liquid chromatography – tandem mass spectrometry (HPLC-MS-MS). Dichlorvos, an organophosphate insecticide was analyzed by capillary-column gas chromatography – mass spectrometry.

5.2.5.1 HPLC-ESI-MS-MS Analysis

APIs in groundwater samples were analyzed by a novel method developed for simultaneous analysis of 61 APIs and their metabolites in multiple environmental matrices (e.g. tap water, surface water and wastewater influent and effluent) as described by Wilkinson et al. (2019). In brief, filtered groundwater samples (Whatman baked glass-fibre filter with pore size 0.45 µm) were analyzed by direct-injection (100 µL injection volume) HPLC-MS-MS. The large volume injection (100 - 5000 µL) approach makes the need for preconcentration of samples prior to analysis unnecessary (Chiaia et al., 2008) and reduces the potential for sample contamination during sample treatment, thereby offering time-saving (Wilkinson et al., 2019) and reproducible analysis (Boix et al., 2014). Chromatographic separation was made by reversed-phase HPLC using a Thermo Dionex UltiMate™ 3000 (Thermo Fisher Scientific™, UK), fitted with a 100-µL sample injection loop and an autosampler maintained at 6 °C. Mobile phase A comprised LCMS-grade water amended with 0.01 M formic acid and 0.01 M ammonium formate for a 1-L volume; mobile phase B was 100% methanol. Chromatographic separation was performed using a ZORBAX Eclipse Plus C18 (3.0 x 100mm, 1.8 µm, 600 bar) analytical column, coupled to a C18 guard column (SecurityGuard™). The gradient elution program was as follows: the percentage of the organic modifier (B) was changed linearly, starting with 10% B and increasing to 40% in 5 min, and then increased to 60% at 10 min, followed by a ramp of B to 100% at 15 min, which was

held till 23 min. The gradient is brought to initial conditions (10%) at 23.1 min. A post run equilibration time for column recalibration was set at 10 min, which resulted in a total runtime of 33.1 min. The flow rate was 0.45 mL min^{-1} and the column temperature was maintained at 40 ^{o}C throughout the analytical run. The collision gas pressure for argon (the collision gas) was set at 2 mTorr. Quantification of analytes was based on internal standard method using a multipoint internal standard calibration range (15 points ranging from 1 to 8000 ng/l) prepared for 33 deuterated internal standards. The HPLC system was interfaced with a triple quadrupole (TQD) (Thermo Scientific™ TSQ Endura) mass spectrometer and analytes were ionized by electrospray ionization (ESI) using heated electrospray source (EASY-Max NG™), operated in the positive ionization mode. Protonated molecular ions of the analytes were fragmented and analyzed using multiple reaction monitoring (MRM) mode. For each compound, collision energy and retention time were optimized for two transition ions, T1 for quantitation and T2 for confirmation of precursor identity (summarized in Table A.C1).

Quantitation of APIs was determined by internal standard (IS) calibration using isotopically labelled pharmaceutical analogues; where identical isotopically labeled standard was not applied, atrazine-d_5 was used to quantify these compounds. Atrazine-d_5 has been used previously as a surrogate compound for many analytes, and has been reported suitable in this role (Furlong et al., 2014). All test standards (≥95% purity) and Deuterated internal standards were purchased from Sigma Aldrich (UK).

5.2.5.2 GC - MS Analysis

Dichlorvos analysis was performed by capillary gas GC - MS using a PerkinElmer Clarus 680 GC coupled to a model 600 MS. Chromatographic separation was performed on Elite-5ms column (30 m length, 0.25 mm I.D., 0.25 µm film thickness). Helium (>99.999% purity) was used as the carrier gas with a column flow rate of 1.0 mL min^{-1}. The injector temperature was 250 ^{o}C and the GC-MSD interface and the ion source temperatures were set at 240 ^{o}C and 180 ^{o}C, respectively.

The GC oven temperature was kept at initial temperature of 50 ^{o}C, followed by the first ramp at 10 ^{o}C min^{-1} to 130 ^{o}C, second ramp at 30^{o} C min^{-1} to 250 ^{o}C, and holding for 3 min, resulting in a total acquisition program of 15 min. Preceding the quantification process was the acquisition of dichlorvos mass spectrum and GC retention time from m/z 50 – 450 using the full scan mode. From these, the base peak ion was selected for quantification and one qualifier ion was used for confirmation. Dichlorvos was quantified by operating the mass spectrometer in the selected ion monitoring (SIM) mode with electron Impact (EI) ionization set to 70 eV. A 5 µL sample was injected in pulsed splitless mode and pulse time was 1.0 min. Quantitation of dichlorvos was determined by external standard calibration method using peak area.

5.2.6 Method Characterization

The HPLC-MS/MS method included a rigorous quality control (QC) plan and validation assessments as described by Wilkinson et al. (2019). Laboratory QC measures involved the use of a laboratory blank along with method and instrumental QC samples dispersed at intervals of 10 injections during analytical runs. The laboratory blank (LB) was used to assess potential contamination with pharmaceutical compounds during sample processing and analysis. LB contained 995 µL high purity reagent water (LCMS-grade) and 5 µL internal standard solution spiked at a concentration of 400 ng/L. Laboratory spike samples fortified with target analytes at a concentration of 80 ng/L were used to monitor method performance.

HPLC-MS-MS method validation included an assessment of the following validation parameters: precision (intra - / inter-day) repeatability, limits of detection (LOD), limits of quantification (LOQ) and recovery. Inter-day / intra-day repeatability was conducted over 3 days, using 10 replicates (n = 10 per concentration) at three concentration levels (10, 100 and 1000 ng/L). Likewise, recovery (analyte response) in LCMS-grade water and in tap drinking water (collected from University of York), was determined at three concentration levels (10, 100 and 1000 ng/L).

Analytical limits (LOD and LOQ) were determined in LCMS-grade water and in drinking water following the statistical procedure described by Sallach et al. (2016) and Wilkinson et al. (2019). In brief, LODs were estimated by multiplying the Grubbs t-test constant for 10 variables by the standard deviation of 10 replicate quantitations of the chemical mixture tested at 1 ng/L (i.e. the lowest calibration level). For each analyte, LOQs were established at two times the LOD and all detected but unquantified concentrations were reported as <LOQ (Table 5.1). In agreement with previously published methods, analyte response range between 60 – 130% and RSD <20% for intra- / inter-day repeatability and precision were considered acceptable (Furlong et al., 2014; Wilkinson et al., 2019).

SPE-GC-MS method was validated based on the determination of linearity, instrument detection limit (IDL) and analyte recovery. Linearity was investigated over a 7-point linear calibration curve at a concentration range of 0.4 µg/L to 64 µg/L. IDL was estimated by a signal to noise (S/N) ratio of 3 using the lowest calibration concentration value (400 ng/L). Recoveries from spring water (100 mL) were determined at spiking level of 1 µg/L (n=7) and subjecting to SPE. Instrumental blanks were randomly dispersed throughout the analytical sequence to verify the absence of interferences and carryover of the method compound.

5.2.7 Statistical analysis

Statistical analysis was performed using Microsoft Excel 2016 software. To determine whether well depth and setback distance were significant predictors of the number of APIs and dichlorvos detected in domestic water wells, regression analysis was conducted based on reported well depths and the measured distance between soakaway pits and the domestic water wells; Differences were considered significant at $p < 0.05$.

5.3 Results and Discussion

5.3.1 Validation and Method Performance

The HPLC-MS/MS method for the quantification of a wide range of APIs was determined to be sufficiently reproducible as assessed by the RSD of intra- and inter-day repeatability and precision. The RSD values were <20% for most determinations, which demonstrate good precision and is desirable in accordance with the USEPA guideline (USEPA, 2016). Recovery from LCMS-grade water and tap water were between 60 – 130%. Analytical limits were within the ng/L range; the limits of detection (LOD) ranged from 0.43 ng/L (ranitidine) to 133.94 ng/L (norfluoxetine) and LOD was < 10 ng/L for 78% of analytes.

The developed GC-MS method provided acceptable sensitivity for dichlorvos. Results were considered positive if they conformed to the GC-MS qualitative criteria (e.g. retention time, mass spectrometric ion-abundance ratios and mass spectral). Quantitation was achieved over a 7-point (0.4 – 64 µg/L) calibration range and good linear regressions (R^2 > 0.995 in all cases) were obtained over the analytical range. Recovery of dichlorvos from SPE was poor at spiking levels of 1.0 µg/L (48.5%) and 2.5 µg/L (30%) and is likely due to inherent losses which are associated with pretreatment using SPE. Previous work has indicated that up to 20 – 40% of analytes could be lost from water during SPE protocols (Leusch et al., 2012; Paíga et al., 2017). The IDL established for dichlorvos with signal-to-noise ratio three times above background using 0.4 µg/L standard calibration solution is estimated to be 223 ng/L. The MDL is established at 0.22 ng/L by dividing the IDL by 1000 to account for 1000 times enrichment of the extracted sample using SPE (i.e. 100 mL spiked sample was reconstituted in 100 µL of hexane prior to analysis).

5.3.2 Application of the analytical methods to groundwater samples from southern Nigeria

The two analytical methods previously discussed were applied to groundwater samples collected from domestic water wells downgradient of septic systems in southern Nigeria. The application of these methods allowed the detection of APIs and a household insecticide (dichlorvos) in groundwater. The sampling design in this study and other published studies (Barnes et al., 2008; Phillips et al., 2015) prioritized wells downgradient of septic systems for sampling as they are potentially more susceptible to contamination from septic effluent discharges. As noted previously, groundwater is an important drinking water source in the study area and indeed other parts of the country.

5.3.3 API occurrence

Of the 53 groundwater samples analyzed, there were 565 individual detections of APIs (Table A.C2); 103 had concentrations below the LOD and were excluded from the calculation of detection frequencies. Excluding results below LODs is similar to the reporting convention used by other studies to avoid reporting false positive detections (Fram & Belitz, 2011). More than half (64%, n=39) of the 61 target APIs were detected in groundwater samples and they comprise a wide range of therapeutic classes, including anti-depressants, antimalarials, antihypertensives, stimulants, anticonvulsants, antihistamines, antibiotics, antifungals, antianginals, anxiolytics, anti-inflammatory, antivirals, analgesics and anti-asthmatics (Table 5.1). All the 53 sampled wells contained detectable levels of at least two APIs with highly variable concentrations among the detected compounds (Fig. 5. 2). The API detected at the highest concentration was the antibiotic sulfamethoxazole, at a maximum concentration of 1253 ng/L; Ketotifen (antihistamine) was detected at the lowest concentration, at a maximum concentration of 1.93 ng/L (Table 5.1).

Table 5. 1 Summary data for APIs analyzed in 53 groundwater samples from southern Nigeria

Compound	CASRN	Uses / Functions	LOD (ng/L)	LOQ (ng/L)	Number of times detected (%)	Median Conc. (ng/L)	Max Conc (ng/L)	Max Conc. (other studies)	Health based guideline value (ng/L)
Amitriptyline	549-18-8	Antidepressant	2.96	5.92	17 (32%)	<LOQ	8.61		
Artemisinin	63968-64-9	Antimalarial	3.37	6.74	3 (6%)	381	684		
Atenolol	29122-68-7	Antihypertensive	2.78	5.55	10 (19%)	<LOQ	8.91	0.8[g]	3,800[h]
Caffeine	58-08-2	Stimulant	15.07	30.31	33 (62%)	123	962	1710[b]	
Carbamazepine	298-46-4	Anticonvulsant	0.74	1.48	32 (60%)	8.84	445	210[c]	
Cetirizine	83881-51-0	Antihistamine	3.13	6.27	10 (19%)	6.94	9.18		
Cimetidine	51481-61-9	Antihistamine	1.77	3.55	19 (36%)	16.7	495	<100[d]	
Ciprofloxacin	85721-33-1	Antibiotic	11.91	23.82	12 (23%)	<LOQ	111	50[f]	
Citalopram	59729-33-8	Antidepressant	1.32	2.64	4 (8%)	<LOQ	3.47		
Clarithromycin	81103-11-9	Antibiotic	14.38	28.77	3 (6%)	90.8	118		
Clotrimazole	23593-75-1	Antifungal	19.76	39.52	12 (23%)	124	205		
Codeine	76-57-3	Opioid Analgesic	0.73	1.46	3 (6%)	4.21	6.04	80[f]	
Cotinine	486-56-6	Nicotine metabolite	7.43	14.86	15 (28%)	24.0	748	60[f]	
Desvenlafaxine	9341-62-8	Venlafaxine degradate	3.40	6.81	4 (8%)	<LOQ	7.90		
Diazepam	439-14-5	Anxiolytic	1.47	2.94	6 (11%)	<LOQ	4.29		
Diltiazem	42399-41-7	Antianginal	0.88	1.76	4 (8%)	<LOQ	2.73	<20[d]	
Diphenhydramine	58-73-1	Antihistamine	5.35	10.71	ND	ND	ND		
Enrofloxacin	93106-60-6	Antibiotic	2.66	5.32	ND	ND	ND		
Erythromycin	114-07-8	Antibiotic	1.06	2.13	2 (4%)	12.8	23.9		
Fexofenadine	83799-24-0	Antihistamine	3.07	6.14	3 (6%)	59.5	66.0		
Fluconazole	86386-73-4	Antifungal	1.57	3.13	ND	ND	ND	>100[g]	
Fluoxetine	54910-89-3	Antidepressant	6.63	13.25	1 (2%)	67.0	67.0		
Gabapentin	60142-96-3	Anticonvulsant	7.63	15.26	5 (9%)	<LOQ	86.8		
Hydrocodone	125-29-1	Opioid analgesic	1.31	2.63	10 (19%)	<LOQ	3.83		

Table 5.1 (Continued)

Compound	CASRN	Uses / Functions	LOD (ng/L)	LOQ (ng/L)	Number of times detected (%)	Median Conc. (ng/L)	Max Conc (ng/L)	Max Conc. (other studies)	Health based guideline value (ng/L)
Itraconazole	84625-61-6	Antifungal	21.84	43.68	ND	ND	ND		
Ketoconazole	65277-42-1	Antifungal	3.03	6.06	ND	ND	ND		
Ketotifen	34580-14-8	Antihistamine	0.68	1.37	8 (15%)	<LOQ	1.93		
Lidocaine	137-58-6	Topical anesthetic	1.20	2.41	16 (30%)	3.34	14.4	>500[g]	
Lincomycin	154-21-2	Antibiotic	0.97	1.94	15 (28%)	10.3	249		
Loratadine	79794-75-5	Anti-histamine	7.25	14.50	ND	ND	ND		
Metformin	657-24-9	Hypoglycemic agent	6.34	12.68	8(15%)	39.4	378		
Metronidazole	443-48-1	Antibiotic, antiprotozoal	5.93	11.85	4 (8%)	14.8	21.5		
Miconazole	22916-47-8	Antifungal	3.90	7.80	ND	ND	ND		
Naproxen	22204-53-1	Anti-inflammatory	16.12	32.24	34 (64%)	<LOQ	234	5580[a]	39,000,000[h]
Nevirapine	129618-40-2	Antiviral	5.05	10.10	ND	ND	ND		
Nicotine	54-11-5	Stimulant	2.54	5.08	ND	ND	ND	50[c]	
Norethisterone	68-22-4	Contraceptive	9.08	18.15	8 (15%)	<LOQ	32.8		
Norfluoxetine	57226-68-3	Fluoxetine metabolite	133.94	267.87	1 (2%)	482	482		
Oseltamivir	196618-13-0	Antiviral	3.33	6.66	8 (15%)	<LOQ	161		
Oxazepam	604-75-1	Anxiolytic	15.68	31.36	ND	ND	ND		
Oxytetracycline	2058-46-0	Antibiotic	2.40	4.80	ND	ND	ND		
Paracetamol	103-90-2	Analgesic	11.54	23.08	32 (60%)	43.9	982.0	120[d]	
Pregabalin	148553-50-8	Anti-seizure	10.02	20.05	ND	ND	ND		
Propranolol	525-66-6	Antihypertensive	7.79	15.59	ND	ND	ND		
Raloxifene	84449-90-1	Anti-estrogen	1.82	3.65	3(6%)	3.67	3.72		
Ranitidine	66357-59-3	Antacid	0.43	0.85	8(15%)	4.09	5.32	<100[d]	
Salbutamol	18559-94-9	Anti-asthmatic	5.03	10.07	1 (2 %)	63.0	63.0	<200[d]	

Table 5.1 (Continued)

Compound	CASRN	Uses / Functions	LOD (ng/L)	LOQ (ng/L)	Number of times detected (%)	Median Conc. (ng/L)	Max Conc (ng/L)	Max Conc (other studies) (ng/L)	Health based guideline values (ng/L)
Sertraline	79559-97-0	Anti-depressant	10.85	21.70	ND	ND	ND		
Sitagliptin	486460-32-6	Anti-hyperglycemic	3.63	7.26	ND	ND	ND		
Sulfadiazine	68-35-9	Antibiotic	114.80	229.60	ND	ND	ND		
Sulfamethoxazole	723-46-6	Antibiotic	4.82	9.65	38 (72%)	39.8	1250	1330[g]	6,000,000[h]
Temazepam	846-50-4	Diazepam metabolite	10.87	21.74	ND	ND	ND		
Tetracycline	60-54-8	Antibiotic	13.34	26.67	ND	ND	ND		
Thiabendazole	148-79-8	Anthelmintic	1.84	3.68	ND	ND	ND	10[5]	
Tramadol	27203-92-5	Opioid analgesic	3.61	7.22	11 (21%)	55.3	491	>100[5]	
Triamterene	396-01-0	Diuretic	2.31	4.63	ND	ND	ND		
Trimethoprim	738-70-5	Antibiotic	1.53	3.06	41 (77%)	4.17	193	580[f]	26,000,000[h]
Tylosin	1401-69	Antibiotic	3.85	7.70	ND	ND	ND		
Venlafaxine	93413-69-5	Antidepressant	4.81	9.61	3 (6%)	5.81	11.8		
Verapamil	52-53-9	Antihypertensive	0.84	1.68	14 (26%)	<LOQ	3.34		

LOD - Limit of Detection; LOQ, Limit of Quantitation; ND, not detected; ng/L, nanogram per liter]
Note: All detected but unquantified concentrations (i.e. detections between the LOD and LOQ) are reported as less than the corresponding numerical value of the LOQ (<LOQ). [a] Carrara et al., 2008; [b] Swartz et al., 2006; [c] Godfrey et al., 2007; [d] Hinkle et al., 2005; [e] Schaider et al., 2014; [f] Verstraeten et al., 2005; [g] Phillips et al., 2015; [h] Bruce et al. 2010

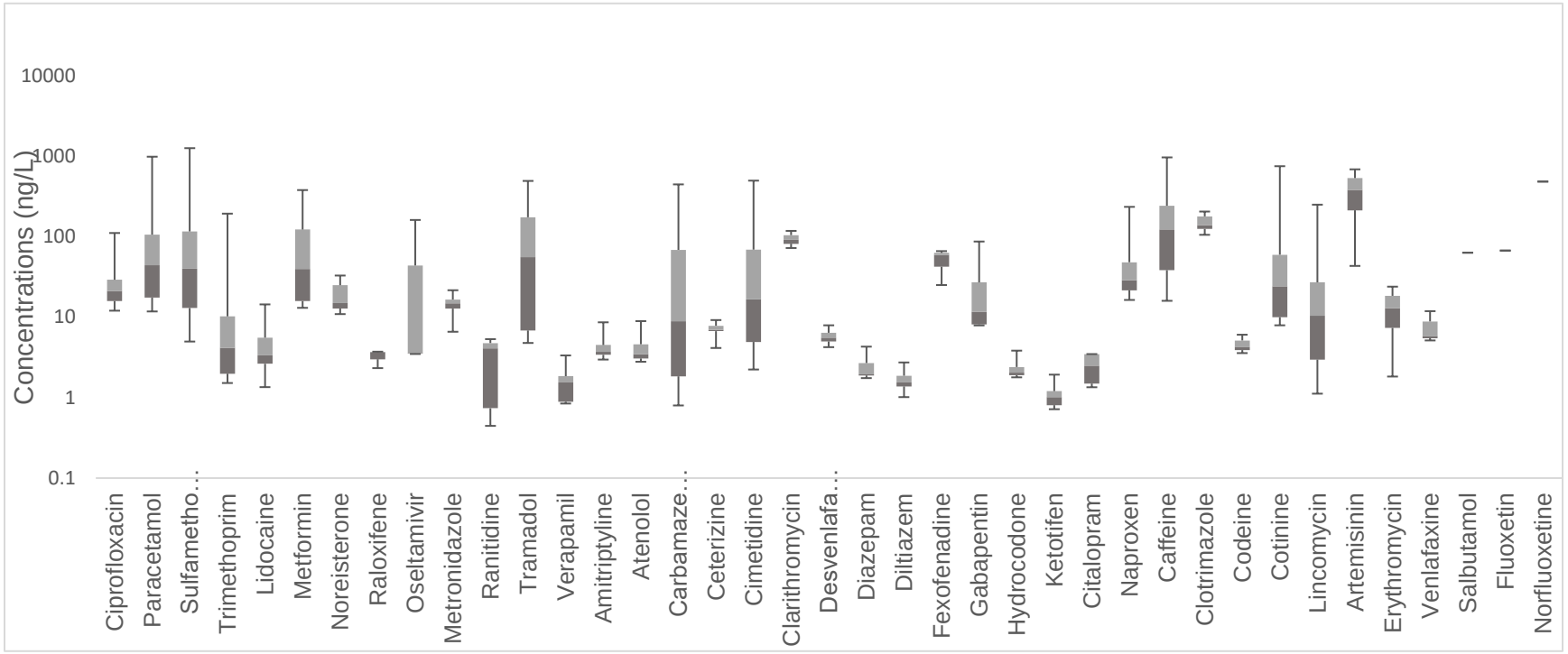


Figure 5.2 Boxplots depicting median, 25th and 75th percentiles of concentrations (ng/L) of APIs detected in groundwater sample from southern Nigeria

The five most frequently detected compounds include trimethoprim (antibiotic, 77%), sulfamethoxazole (antibiotic, 72%), naproxen (anti-inflammatory, 64%), caffeine (stimulant, 62%) and paracetamol (analgesic, 60%); interestingly, these compounds were among the most frequently detected compounds in groundwater sites affected by septic systems in the United States and Canada (Carrara et al., 2008; Schaider et al., 2014; 2016; Hinkle et al., 2005; Verstraeten et al., 2005; Godfrey et al., 2007; Phillips et al., 2015; Katz et al., 2010; Dougherty et al., 2010). The high detection frequency of target compounds in domestic water wells demonstrates that effluent from septic systems is a significant source of APIs to groundwater and this finding is consistent with existing research which reports the ubiquitous nature of pharmaceuticals in wastewater receiving environments, particularly in groundwater and surface water (Heberer, 2002).

Mixtures were common, with 2 or more APIs detected in all the sampled wells and 5 or more APIs detected in 45 (85%) of the 53 wells. The co-occurrence of sulfamethoxazole and trimethoprim in most of the sampled wells is expected as both APIs are most commonly used in combination for treating urinary tract and ear infections. While an increasing amount of data are now becoming available on occurrence and concentrations of APIs in drinking water sources, the potential toxicological effects of individual compounds or mixtures remain largely unknown (Jones et al., 2004;) but potential adverse consequences on humans due to additive effects of API mixtures at environmentally relevant concentrations (>100 ng/L) (Lapworth et al., 2012) have been highlighted as an actual risk (Pomati et al., 2008).

Notable differences among groundwater samples and between the two subareas (PHMA and ENMA) were observed both in the number of detections and the concentrations of the APIs and may be attributed to differences in geological settings. The number of API detections in groundwater samples ranged from 7 to 22 detections in the shallower wells from EMNA and 2 to 15 detections in the deeper wells from PHMA (Figure A.C1). Comparing the total concentrations

of APIs ($\sum pharma_{GW}$) among groundwater samples (on a per well basis) and between the two study locations may help put the magnitude of and differences in the measured concentrations into context. $\sum pharma_{GW}$ in groundwater samples ranged from 23 ng/L to 2240 ng/L, with elevated concentrations observed in wells from ENMA; $\sum pharma_{GW}$ ranged from 215 ng/L to 2240 ng/L in groundwater samples from ENMA and 23.5 ng/L to 1060 ng/L in groundwater samples from PHMA. $\sum pharma_{GW}$ exceeded 1 µg/L in 9 of 16 (56%) wells from ENMA and in one of 37 (3%) wells from PHMA. $\sum pharma_{GW}$ values may not reflect actual API concentrations considering that estimates do not include other nontarget APIs that may be present but not analyzed or those occurring below the LOD. Differences in the depth of wells in the two subareas may explain the higher $\sum pharma_{GW}$ that was observed at the ENMA study site. Wells in ENMA are generally shallow (<15 m), and in the study sites, average well depth was 9.5 m and ranged from 6 to 13 m; by comparison, wells in PHMA are much deeper, and in the study sites, average well depth was 30 m and ranged from 24 to 36 m. The difference in well depth suggests that there may be a limited degree of attenuation at sites in ENMA than in PHMA and these findings agree with previous studies. In an earlier study, Barnes et al. (2008) observed significantly higher detection of pharmaceuticals in shallower wells. In California, USA, Fram and Belitz, (2011) found the deep nature of boreholes to be partly responsible for the low detection frequencies (2.3%) for pharmaceutical compounds in groundwaters used for public drinking water supply. According to Carrara et al. (2008), reduced depth to the water table (which is the case for shallow wells) means reduced transport times in the vadose zone which provides contaminant breakdown through aerobic oxidation;. the consequence is that the more persistent and more mobile contaminants can easily get to groundwater. In addition to differences in well depth, the characteristics of the geological formations at ENMA may also contribute to the enhanced transport of APIs to the underlying aquifer. The geological formation in ENMA is fractured and has been found to provide a substantial seepage pathway for contaminant transport (Obiadi et al., 2016), suggesting that APIs from septic system leachates may be easily transported in the subsurface through these

fractures. Other factors including septic system design and effluent loading rate (which can lead to faster flow rate and reduced residence times) can contribute to the degree of attenuation of pharmaceutical compounds and other OWCs (Carrara et al., 2008) but have not been explored in the current study.

When compared with previous studies, notable differences were observed in the levels of APIs detected in groundwater samples. Maximum concentrations of nine pharmaceuticals detected in this study (e.g. atenolol (antihypertensive), carbamazepine (anticonvulsant), cimetidine (antihistamine), ciprofloxacin (antibiotic), cotinine (nicotine metabolite), paracetamol (analgesic) and tramadol (opioid analgesic)) exceeded the maximum concentrations reported in previous studies (Table 5.1) (Schaider et al., 2014; 2016; Godfrey et al. 2007; Hinkle et al., 2005; Verstraeten et al., 2005; Phillips et al., 2015; Katz et al., 2010; Dougherty et al. 2010). It is important to mention that maximum sulfamethoxazole and trimethoprim concentrations exceeded maximum concentrations in 6 of 7 previous studies reporting their occurrence in groundwater in the United States; this is likely due to one or more factors (Conn et al., 2006) including high usage mass of these antibiotics, poorly functioning septic systems (which reduce treatment efficiency) or poor treatment of septic effluent discharges during vadose zone transport in the study area. Furthermore, contrary to previous findings which have demonstrated that compounds observed with the highest frequency are not often found in the highest concentrations (Kolpin et al., 2002; Barnes et al., 2008), in the current study, four APIs with the highest concentrations were also among the most frequently detected compounds: sulfamethoxazole (1250 ng/L; 38%), followed by paracetamol (982 ng/L; 32%); caffeine (962; 33%) and cotinine (748 ng/L; 15%).

Twenty-two APIs were not detected in groundwater samples in this study and three were detected in less than 3% of samples and include salbutamol, fluoxetine and norfluoxetine; artemisinin, an antimalarial agent was detected in 3 of the 53 sampled wells in this study (Table 5.1) and to the best of the author's knowledge, this is the first time artemisinin has been detected in groundwater

affected by septic systems. Five of the target compounds not detected in this study (e.g. diphenhydramine, enrofloxacin, nicotine, thiabendazole and fluconazole) have been reported in previous studies in the United States (Phillips et al., 2015; Hinkle et al., 2005; Godfrey et al., 2007; Verstraeten et al., 2005). It needs to be said that non-detections do not necessarily indicate a complete absence of an API as these compounds may undergo transformation or degradation from metabolic and natural attenuation processes (Boxall et al.,2004) during treatment in septic tanks and vadose zone transport (Conn et al., 2006). It has been suggested that non-detections in samples may be a result of parent compounds being completely attenuated, partially attenuated (e.g. to levels below analytical detection capabilities) or due to absence from the source (Barnes et al., 2008). For example, in the current study, nicotine was not detected in any of the sampled wells, but its metabolite, cotinine was detected in 28% (n=15) of sampled wells at concentrations ranging from 7.90 ng/L to 748 ng/L.

In general, EOCs detected in environmental samples do not always occur in significant concentrations (>100 ng/L) owing to natural attenuation and dilution mechanisms (Lapworth et al., 2012) and this is similar to the findings in this study. Many of the API detections were at low-level concentrations, with 375 of 462 detections below 100 ng/L. Only one API exceeded a maximum concentration of 1 µg/L (Sulfamethoxazole; 1250 ng/L). Four of 61 compounds have established drinking water guidelines and none of these compounds exceeded these limits (Table 5.1); the lack of established drinking water standards for most APIs generally hinders the interpretation of monitoring results from a human health perspective (Barnes et al., 2008).

Detection frequency varied widely among pharmaceutical classes (Figure 5.3), with antibiotics being the dominant (25%) API class and consisted of 7 compounds including ciprofloxacin, clarithromycin, erythromycin, lincomycin, trimethoprim, sulfamethoxazole and metronidazole; this is followed by analgesics > antihistamines > anticonvulsants > anti-inflammatory > stimulants > antidepressants and antihypertensives with detection frequencies in the range of 5 to 12%.

Eleven other pharmaceutical classes were less dominant, with detection frequencies of 4% or less (Fig. 5.3).

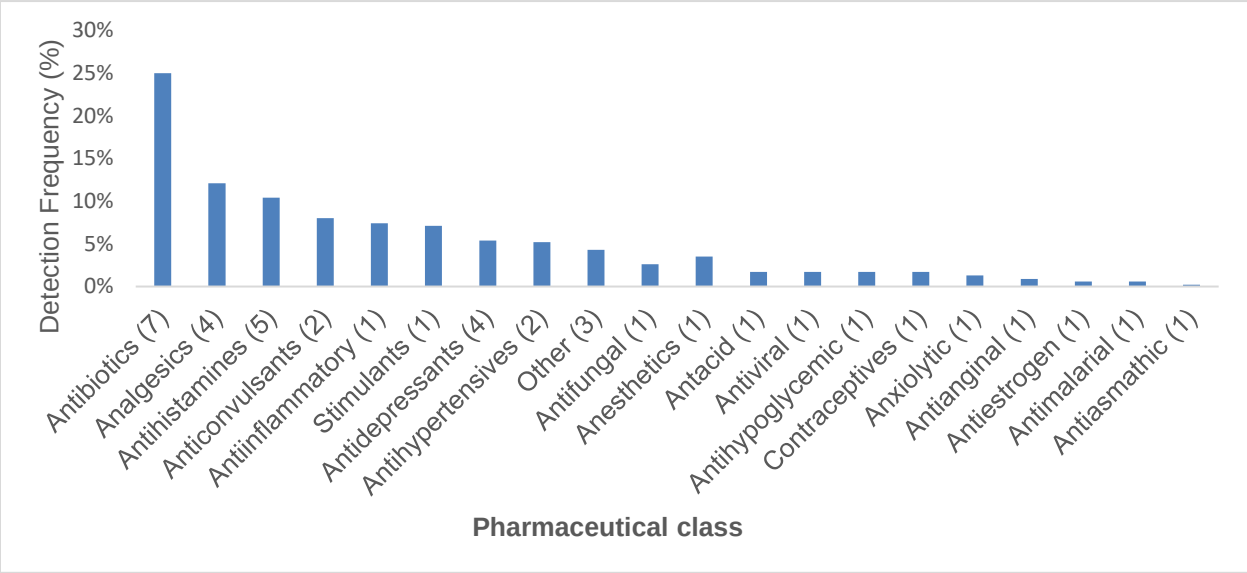


Figure 5. 2 Frequency of detection by pharmaceutical class

The widespread detections of antibiotics in various environmental compartments have led to concerns that antibiotic-resistant pathogens can evolve following selective pressure from antibiotics in the environment (Bengtsson-Palme & Larsson, 2016). Thus, the measured environmental concentrations (MEC) of six antibiotics detected in groundwater samples in this study were compared with their respective predicted no effect concentration (PNEC) for resistance selection (Table 5.2) estimated by Bengtsson-Palme & Larsson. (2016). Results show that the highest measured concentration (MEC_{max}) of each antibiotic was below the estimated PNEC for selection of resistance, suggesting that the presence of these antibiotics in groundwater does not pose any risk of resistance promotion.

Table 5. 2 Comparing MEC of antibiotics in groundwater samples to PNEC for resistance selection

Compound	MEC Median (µg/L)	MEC Max (µg/L)	MIC (µg/L)	PNEC (µg/L)
Ciprofloxacin	0.0212	0.0111	1	0.064
Clarithromycin	0.0908	0.118	2	0.25
Erythromycin	0.0128	0.0239	8	1.0
Metronidazole	0.0148	0.0215	2	0.125
Sulfamethoxazole	0.0398	1.25	125	16
Trimethoprim	0.00417	0.193	8	0.5

where MEC is the measured environmental concentration; MIC is the minimal inhibitory concentration which represents the upper boundaries for selective concentrations (i.e. lowest MIC); PNEC is the predicted no effects concentration for resistance selection (Bengtsson-Palme & Larsson, 2016).

5.3.4 Dichlorvos occurrence

Of the 20 samples analyzed for dichlorvos and with positive detections of APIs, 60% (n=12) also contained dichlorvos (household insecticide). Dichlorvos concentrations in groundwater samples were low and ranged from 1.88 ng/L to 68.0 ng/L, which are below the EU drinking water maximum allowable concentration of 0.1 µg/L for pesticides (European Commission, 1980). The presence of dichlorvos in groundwater samples may be attributed to its intensive use in Nigeria and its physicochemical properties. Dichlorvos is the active ingredient widely used in locally formulated insecticides for the control of household pests in many Nigeria households (Kanu et al., 2016) and for the protection of stored products from insects by farmers and traders. Dichlorvos has a high aqueous solubility (18000 mg/L) and a low octanol-water partition coefficient (log K_{ow} 1.9) (Anyusheva et al., 2012) and with a soil adsorption coefficient (log K_{oc}) of 1.4 (Teunissen-Ordelman & Schrap, 1997), it is a potentially mobile pollutant in soils (McCall et al., 1980). Although dichlorvos is highly volatile (vapor pressure 2100 mPa) (Anyusheva et al., 2012) and as such, volatilization from soils is the primary dissipation pathway (EPA, n.d.), once dissolved, the potential to enter the gas phase is low (Gautier et al., 2003). The low level detections of dichlorvos observed in this study may be due to its rapid degradation and

mineralization in soils through aerobic soil metabolism and abiotic hydrolysis (EPA, n.d.). Dichlorvos has been less widely reported in literature. Dichlorvos was found to occur in STE and groundwater samples from La Pine, Oregon, at <RL (1µg/L) (Hinkle et al., 2005). Because dichlorvos degrades rapidly in soil, it is suggested that future analysis should include the analysis of major dichlorvos degradates in groundwater. Its absence in environmental samples from many countries may be explained by the declining consumer use of dichlorvos in countries like the United States since the early 1990s (ATSDR, 1993) and the 'not approved for use' status in the European Union (EU) following concerns about its acute toxicity (EU, 2012).

5.3.5 Correlation between detections and drivers of wastewater impact

The sampled domestic water wells are characterized by different depths (average depth 24 m; range 6 -36 m) and setback distances also varied across sites (e.g. average distance 15 m; range 2 – 36 m) (Table A.C3). Generally, it is expected that shallow domestic water wells located in close proximity to septic system drain fields or seepage pits would have a higher pollution risk as they would be more vulnerable to contamination by septic system leachates (Bremer and Harter, 2012; Schaider et al., 2011) but in this study there was a weak correlation between well depth and the number of detections of APIs (i.e. pollution risk) and there was no relationship between the number of API detections and setback distance. Linear Regression was used to determine whether well depth and setback distance are good predictors of the number of detections of target compounds across the sampled wells. Regression analysis shows the relationship between well depth and number of detections is statistically significant ($p<0.05$) but based on the R-squared value (which indicates how much of the variability in the number of detections is explained by well depth), only 15 percent of the variability in the number of detections can be explained by well depth; there was no statistically significant relationship ($p>0.05$) between setback back distance and the number of detections, which means that the number of target compounds in wells does not correlate to setback distance. The low R-squared value and the lack of correlation between

the number of detections and setback distance, suggest that well depth and setback distance do not explain much of the variability in the number of detections across the sampled wells and that other drivers of wastewater impact (e.g. septic system density) are likely influencing vulnerability of groundwater to septic system leachates.

Several septic system density related studies have reported significant correlations of septic system density to the number and concentrations of contaminants observed in test samples. In a study to determine the susceptibility of surface water ecosystems to contamination from groundwater impacted by septic systems, greater number and higher concentrations of OWCs were found in samples from higher residential density areas (Standley et al., 2008). Whitehead & Geary (2000) investigated the potential impact of septic systems on Australian groundwater and concluded that shallow aquifers are at greater risk of contamination in high density areas with small lots. In a report to the United States congress, the US EPA considered septic system density to be the most important control of pollution risk from septic systems and specified that more than 1 septic system in 16 acres constituted a risk factor of groundwater contamination (U.S Environmental Protection Agency., 1977). A review of septic system related water quality studies carried out in several locations in the United States confirms the consensus that excessive septic system densities can degrade water quality (Nielsen, 2016) and this may be the case for Nigeria. As stated earlier, the average housing density in many urban and suburban areas in Nigeria is 6 to 8 dwellings per acre, with each dwelling relying on individual septic systems to treat and dispose sewage; this results in an estimated spatial septic system density of 6 to 8 systems per acre, which exceeds the critical maximum septic system density of 1 system per 16 acres recommended by the US EPA. The critical maximum density refers to the maximum number of septic systems per area that would not overstretch the purifying capacity of soils and the dilution potential of aquifers (Bremer & Harter, 2012). Given that in this study, wells in closely built-up areas (i.e. high spatial septic system density) were prioritized for sampling (Fig.5.1), it is

reasonable to assume that the excessive septic system density in the study area may have contributed substantially to the number and concentrations of the target compounds observed in most of the sampled wells. A septic system density study is therefore required to predict reasonable septic system densities for the protection of groundwater quality in Nigeria.

5.4 Conclusion

This is the first study to provide baseline information on the occurrence of dichlorvos and APIs in groundwater affected by septic systems in Nigeria. The result of this study demonstrates the ubiquitous nature of APIs in the environment and contributes to the much needed global environmental occurrence data for pharmaceutical compounds, particularly in a region with limited research on pharmaceutical pollution and significant knowledge gaps regarding environmental exposure to pharmaceuticals. This study provides a foundational list of APIs for future groundwater monitoring programs in Nigeria and it is anticipated that this study will shape the direction and priorities for future research in pharmaceutical occurrence, fate and risks in Nigeria and other countries in Africa. The high detection frequencies of several APIs in domestic water wells used as a drinking water source suggest that exposure to these compounds through drinking water intake is likely to occur considering that water is often consumed untreated. In the next section (Chapter 6), the potential risk of indirect exposure to APIs through drinking water intake will be assessed using the maximum MEC values generated in this chapter. The use of monitoring data, which represent real-world concentrations, are invaluable exposure parameters and their inclusion in risk assessment helps to reduce uncertainties associated with exposure and risk assessments.

Chapter 6

Human health risk assessment of indirect exposure to active pharmaceutical ingredients in drinking water supply in Nigeria

6.1 Introduction

The occurrence of APIs in drinking water supplies has led to concerns about public health safety. A wide range of APIs have been detected at trace levels (nanogram to microgram per liter range) in source water across the United States including surface water (Kolpin et al., 2002), groundwater (Godfrey et al., 2007; Carrara et al., 2008), drinking water wells (Schaider et al., 2014; 2016) and treated drinking water (de Jesus Gaffeny et al., 2015).

Wastewater treatment processes have been identified as a major contributing source of APIs to the environment due to metabolic excretion and improper disposal of unused medications through toilet and sink (Glassmeyer et al., 2009; Bound and Voulvoulis, 2005), in addition to the inherent treatment inefficiencies of wastewater treatment systems (Conn et al., 2006). In many low-to-middle income countries, usually lacking access to centralized sewage collection systems, conventional onsite wastewater treatment systems (OWTSs) which offer a cheap alternative to municipal wastewater treatment plants (WWTPs) (Lusk et al., 2011a), are a primary source of groundwater contamination and a potential source of pharmaceutical exposure, as they are designed to continuously discharge partially treated effluent to the surrounding soil environment (Carroll et al., 2006). APIs are biologically active substances, intentionally formulated to interact with the human body and modulate biochemical activity even at low concentrations (Kumar et al., 2010; Boxall et al., 2012). Thus, non-therapeutic exposure to APIs through drinking water intake could pose a potential risk to human health and has become an issue of concern (Bercu et al., 2008) . Environmental exposure to APIs may be significant in a country like Nigeria, where there

is a huge reliance on septic systems for sewage treatment and on the underlying aquifer recharged by these systems as a drinking water source. In Nigeria, over 70% of households rely on domestic water supply wells to meet their water needs, and in most cases, water is consumed without advanced treatment. Evidence of the impact of septic systems on groundwater quality has been well documented as many studies including those presented in Chapter 5 have reported measurable concentrations of a wide range of wastewater contaminants in groundwater affected by septic effluent discharges (Standley et al., 2008; Del Rosario et al., 2014; Phillips et al., 2015; Schaider et al., 2014; 2016; Katz et al., 2010).

The persistence of APIs in source water and the presence of residuals in finished drinking water has resulted in concerted efforts to assess potential human health risks from exposure to contaminated drinking water. Interestingly, most of the risk assessment studies concluded that there may be no appreciable risks arising from low level pharmaceutical exposure through drinking water intake (Cunningham et al., 2009; Schulman et al., 2002; Schwab et al., 2005; Houtman et al., 2014). It is however important to mention that for most studies, assessment is based on concentrations levels in treated drinking water. It is widely acknowledged that the huge contrast between observed concentrations of APIs in source water and potable water supply is due to the efficacy of a range of water treatment processes (Webb et al., 2003; Andreozzi et al., 2002; Ternes et al., 2002; Huber et al., 2003). This indicates that the suppositions of no appreciable risk drawn from these studies may be underestimating risk of harm from API exposure through drinking water in areas where water is consumed without advanced treatment. The aim of this study therefore, was to assess the possible health risks associated with exposure to APIs in untreated drinking water from non-sewered communities.

API occurrence data, which reflect the actual levels of exposure were available from a groundwater monitoring campaign in non-sewered areas in southern Nigeria reported in Chapter 5. Risk was assessed by benchmarking exposure (measured environmental concentrations

(MECs)) with acceptable daily exposure limits (ADEs). The utilization of the concept of ADEs provides a holistic and consistent scientifically acceptable methodology for the establishment of a health-based limit for APIs (Sargent et al, 2013).

6.2 Materials and methods

The evaluation of potential human health risk of APIs in source water comprised of three general steps. First, target APIs were selected for evaluation; second, acceptable daily exposure value was calculated for each API and the underlying principle is comparable to the 'Margin of Safety' approach used to establish occupational exposure levels (OELs) for pharmaceuticals, acceptable daily intakes for food contaminant, and other health-based limit values. Finally, measured environmental concentrations (MECs) were identified and compared to ADEs for drinking water intake. Each of these steps is described in more detail below.

6.2.1 Selection of compounds for evaluation

Twenty-nine human use APIs evaluated in this study were selected using data from groundwater monitoring studies in non-sewered communities in Nigeria (Chapter 4). The APIs, which belong to 13 pharmacological classes exhibit a broad range of action and pharmacology. Nicotine and cotinine (nicotine metabolite) were excluded from analysis due to limited data availability to assess risk using the current risk assessment methodology. Clotrimazole, designed for local administration (e.g. dermal use) was excluded due to limited data on systemic effects. Lidocaine and lincomycin, which are delivered through the intravenous route were not included due to limited bioavailability data for the derivation of route-specific ADE values. APIs detected less frequently (n=<3; <5%) in domestic water wells, including salbutamol, fluoxetine, norfluoxetine (metabolite of fluoxetine) and raloxifene were excluded from the current assessment. Although for many APIs, the potential exists for additive, antagonistic or synergistic drug interactions, this assessment was carried out as a chemical-specific risk assessment, which requires the evaluation of individual

APIs; hence, it does not account for the potential impact of exposure to API mixtures on human health

6.2.2 Collection of preclinical and clinical data for hazard characterization

Preclinical and clinical data were obtained from numerous sources including Drug Reference handbooks (e.g. Martindale complete drug reference), product monographs and toxicology summary from manufacturers; toxicology data network (TOXNET); Hazardous substances data bank (HSDB), National Library of Medicine literature search engines (e.g. PubChem), DrugBank, Material Safety Data Sheets (MSDS) and peer reviewed literature. A wide range of preclinical and clinical data from these sources were evaluated for each API (e.g. pharmacokinetic, pharmacodynamic, toxicokinetic and toxicodynamic data) required for establishing ADEs. Table 6.2 lists the selected APIs and their therapeutic uses.

6.2.3 Development of ADEs

The ADE represents a substance specific-dose that is unlikely to cause any adverse health effect if an individual is exposed, by any route, at or below this dose every day for a lifetime (EMA, 2014). Thus, the derivation of ADEs for APIs as a potential contaminant in drinking water aims to reduce API exposure to a dose that has no adverse health effects to the potentially exposed population, including healthy adults, as wells susceptible subpopulations (e.g. children, the elderly and gravely ill individuals) (Sussman et al., 2016). This follows the presumption that pharmaceuticals optimized to provide therapeutic benefits to the intended individual are without benefits but with potential risks of an adverse health outcome following unintended exposure to pharmaceuticals (Bercu et al., 2016) e.g. through drinking water consumption

The scientific basis for the derivation of ADEs is detailed in various guideline documents (e.g. European Medicine Agency, 2014; FDA, 2004) and a harmonization approach has been discussed in a number of published literature (Bercu et al., 2016; Sussman et al., 2016; Reichard

et al., 2016 Hayes et al., 2016). Briefly, establishment of an ADE is a multi-step approach involving: i) Hazard characterization through an extensive review of preclinical and clinical data for the APIs. ii) assessment of the dose-response relationship to determine the clinical or toxicological endpoint(s) of the API which will serve as the critical effect(s) for deriving the ADE; iii) determination of the point-of-departure (POD), which is the starting dose for the calculation of an ADE; and iv) calculation of the ADE by applying 'adjustment', 'uncertainty' or 'safety' factors to account for various sources of variability and uncertainty in the POD as it compares to the target population. Animal studies preclinical data were reviewed for various endpoints including acute, chronic, developmental, reproductive, mutagenic and carcinogenic endpoints. The clinical data from human studies were reviewed for pharmacological and adverse (or critical effects). The 'critical effect' when determined from an animal study is 'the most sensitive adverse effect that is considered relevant to humans'' (Naumann et al., 2008), and in the context of ADE derivation, both intended pharmacological activity and unintended toxicity are considered adverse; thus more than one candidate critical effect may be selected for an API with emphasis on the critical effect that is most relevant to the target population (Bercu et al., 2016). If similar effect occurred in both humans and animals, the human study was selected for the POD (Dourson et al., 2001). The target population can be protected by applying an appropriate 'margin of safety' to a POD for a specific critical effect (Sussman et al., 2016). The POD is typically the point that corresponds to an estimated no effect level or low effect level on a toxicological dose response curve derived from animal or clinical data. Considerations for the selection of appropriate POD for the derivation of ADEs are detailed in Bercu et al. (2016). Briefly, the preferred POD for deriving ADE for APIs is the no-observed-(adverse) effect-level (NOAEL), which is a dose at which there is no 'clinically relevant' pharmacological response when ingested by an unintended individual (i.e., in the event of a nontherapeutic exposure). For many APIs however, the LOAEL is used in the absence of a NOAEL, and represents an 'adverse dose', which is the lowest observed dose resulting in a statistically and toxicologically significant response as compared to a control group (i.e. the lowest

dose resulting in an effect of human relevance) (USEPA, 2002a). In addition, clinical dosing information can be used in the selection of a POD by applying the Lowest Therapeutic Dose (LTD) and when available, pharmacodynamic (PD) data from clinical trials are valuable for the selection of POD at subtherapeutic doses (i.e. a dose level showing no 'clinically relevant' changes) (Bercu et al., 2016). For the current evaluation, the LTD in the most sensitive subpopulation is important to include as the POD in calculating the most protective ADE for an API as a potential contaminant in drinking water. This group, compared to the general population are potentially more susceptible to nontherapeutic exposure to APIs due to their age, sex, genetics and pre-existing diseases (Sussman et al., 2016).

To calculate the ADEs, uncertainty factors (UF) are applied (Equation 6.1) to reduce the starting dose (i.e. POD) to a 'safe' dose level (Sussman et al., 2016), which in the context of this study, is a dose assumed to pose no appreciable risk to human health following lifetime exposure via drinking water intake.

$$ADE\ \left(\frac{mg}{day}\right) = \frac{POD * BW}{UFC * MF * PK} \qquad (6.1)$$

Where ADE = acceptable daily exposure; POD = point of departure; UFC = composite uncertainty factor; BW = body weight; MF = modifying factor; PK = pharmacokinetic adjustment factor.

If available, NOAEL used as a POD is corrected for body weight (BW) unless a dose in mg/day is applied (e.g. a LOAEL or LTD Level) and the body weight factor becomes unnecessary. A composite uncertainty factor (UF_C) applied to the POD accounts for the following sources of uncertainty: Intraspecies Differences (UF_H); Interspecies Differences (UF_A); Sub-chronic-to-Chronic extrapolation (UF_S); LOAEL-to-NOAEL extrapolation (UF_L); and Database Completeness (UF_D); a modifying factor (MF) allows the use of professional judgement to account for residual

uncertainties not addressed by the UF_C (e.g. severity of effects); however, Sussman et al. (2016) cautions that care be taken in the consideration of individual factors to avoid accounting for a factor more than once, which may result in unreasonably large composite factors and a concomitant increase in the uncertainty of the derived ADEs. The pharmacokinetic (PK) factor in Equation 6.1 enables the integration of chemical specific adjustment factors (CSAFs) into the derivation of ADEs. Thus, where chemical specific data are available, PK may be considered and the ADE adjusted to account for differences in bioavailability (α) between different routes of exposure and/or adjusted for steady-state plasma concentrations that are higher due to accumulation following repeated exposures when compared to single exposures from a short-term critical study (Dolan et al., 2005; Reichard et al., 2016). The latter is based on the principle that chronic effects may result from repeated exposure to a substance at doses lower than the NOAEL obtained from a study of short duration (Sussman et al., 2016). The UFs described in Table 6.1 are based on adjustment factors and scaling approaches recommended in different guidance documents (ICH Q3C, 2011; US FDA, 2005; ECHA, 2012; EMA, 2014) for use in the derivation of health-based limits. Table 6.2 describes the implementation of these concepts through the incorporation of available clinical and nonclinical data for individual APIs.

Table 6. 1 Rationale for the application of uncertainty and modification factors in the derivation of ADEs

Factor	Area of Uncertainty	Basic Principle	Considerations for UF selection	References
UF_H	Average Human to sensitive Human	Adjusts the POD for the toxicokinetic (TK) and toxicodynamic (TD) differences between the average human and the most sensitive applicable subpopulation	**10** Recommended when TK and TD data are not available or when product labeling or mechanism of action identifies there is likelihood and severity of effects that might occur in sensitive subpopulation **3** Recommended when effect is therapeutic and there is little difference between the median and minimally effective dose **3** Recommended when using an adjusted LOEL, NOEL or therapeutic dose specific to a sensitive sub-population **1** Recommended when sufficient post-marketing data indicate the absence of specific and particularly sensitive individuals or when using a NOEL for a presumed non-adverse effect with little or no clinical significance	1, 4, 5, 6
UF_A	Animal to Human	Adjusts for differences in sensitivity between animals and the average human, when POD is based on animal studies	**10** Recommended when no human data are available **4** Recommended to account for animal to human variability in toxicokinetics **3** Recommended when ADME data are similar for multiple species, including humans or non-human primates **2.5** Recommended to account for animal to human variability in toxicodynamics **1** Recommended when derivation is based on human data	
UF_L	LOAEL-to-NOAEL	Adjusts for uncertainty in the value of the POD as an estimate of the threshold for the onset of effects, if based on a LOAEL rather than a benchmark dose or a NOAEL	**10** Recommended when NOAEL is not available **3** Recommended when the LOAEL is a therapeutic response, operative only in a disease state **1** Recommended when the LOEL is associated with a homeostatic response or a mild effect on a clinical pathology parameter with no other effects or minor changes in biomarkers (e.g. Enzyme inhibition; gene expression) without changes in clinical or functional parameters (i.e. the LOEL is a NOAEL)	

Allometric scaling approach for interspecies extrapolation

Species	ICH Q3C (2011)	US FDA (2005)	REACH (ECHA, 2012)
Mouse	12	12.3	7
Rat	5	6.2	4
Rabbit	2.5	3.1	2
Dog	2	1.8	1.4
Monkey	3	3.1	2
Other Species	10 or $BW^{0.67}$	$BW^{0.67}$	$BW^{0.75}$

Table 6.1 (Continued)

Factor	Area of Uncertainty	Basic Principle	Considerations for UF selection	References
UF_S	Short-term to Long-term Exposure	Adjusts for the possibility of identifying a lower POD when extrapolating from a study of shorter duration	**10** Recommended when observed effects increase in severity and / or occur at low doses over time **6-10** Recommended for Sub-acute (28-day study) to Chronic exposure **2-3** Recommended for Sub-chronic (90-day study) to Chronic exposure **1** Recommended for a nine-month study in non-rodents; six-month study in rodents **1** Recommended when human study data for longer administration are available and no increase of effects or accumulation is observed over time **1** Recommended when chronic animal data are available and no increase in effects is observed over time	1, 2, 3, 7
UF_D	Database Completeness	Adjusts for the possibility that a study not yet conducted could have a lower NOAEL than the study used in the current POD	10, 3 or 1, or a number smaller than 1 are recommended for the professional judgement on the quality of data available on a compound **3-10** **Recommended when important specialized studies (e.g. reproductive toxicity or developmental toxicity or chronic and carcinogenicity) are not available** **>1** Recommended when acute and repeat dose toxicity data via relevant route of exposure are not available **>1** Recommended when data on pharmacokinetics and pharmacodynamics from clinical and nonclinical studies are not available **>1** Critical studies used small number of animals or group **1** Recommended when full set of pharmacological and toxicological data are available **1** Recommended when a compound is non-genotoxic and shows no proliferation effects in animal studies and a very sensitive pharmacodynamic endpoint has been selected as POD **1** The absence of data is mitigated by the results on a compound of similar structure and responses	4, 5, 6, 7, 8

Table 6.1 (Continued)

Factor	Area of Uncertainty	Basic Principle	Considerations for UF selection	References
MF	Considerations for the application of MFs **1** the slope of the dose response curve **2** the choice of the critical effect **3** the severity of effects **4** route-to-route extrapolation **5** identification of susceptible subpopulation **6** clinical significance of the critical effect **7** reversibility of the critical effect **8** overall quality of the database **9** relevance of the critical effect to the target population **10** similarity or differences with related chemicals; **11** lack of independence between individual uncertainty factors	Adjusts for the possibility of residual uncertainties not covered or clearly addressed by other adjustment factors listed above	**<1-10** **Recommended for professional judgement on the overall quality of the database and relevance of available studies to human health risk assessment.** **1** **Fetal toxicity associated with maternal toxicity** **5** Fetal toxicity without maternal toxicity **5** Teratogenic effect with maternal toxicity **10** Teratogenic effect without maternal toxicity	1, 4, 5, 6,

1- ICH Q3C, (2011); 2-ECHA, (2012); 3-EMA, (2014); 4-Sussman et al. (2016); 5-Dankovic et al. (2015); 6-Bercu et al. (2016); 7-US FDA, (2005); 8 - Schwab et al. (2005); ICH - The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; ECHA -European Chemicals Agency; US FDA - United States Food and drug Administration.

6.2.4 Estimating exposure to APIs from drinking water intake

Assessment of exposure to APIs through drinking water was based on maximum measured environmental concentrations (MEC) from a groundwater monitoring campaign for southern Nigeria (Chapter 4) and daily drinking water intake of 2 liters per day (assumed standard for a 70 kg adult). Where concentrations are below detection, half the limit of quantitation (1/2 LOQ) was used to estimate intake (Schwab et al., 2005). The current assessment adopts a conservative approach that water is consumed untreated, that no degradation of APIs occurs prior to use and that exposure occurs at the highest concentration of individual APIs in drinking water.

6.2.5 Risk Calculation

The human health risk of exposure to APIs through drinking water intake was assessed by comparing the maximum MECs or ½ LOQ of individual APIs with ADEs (Equation 6.2).

$$HQ = \frac{Exposure\ (MEC\left(\frac{ng}{l}\right) * \frac{2l}{day}}{ADE\left(\frac{mg}{day}\right) * 1000000} \qquad (6.2)$$

Where HQ is the hazard quotient (unitless); Exposure to APIs through drinking water is the product of measured environmental concentration (MEC) of APIs in drinking water (ng/L) and the daily water intake of 2 liters per day for a 70 Kg adult; ADE represents acceptable daily exposure; 10^6 is the unit of conversion and LOQ is the reporting limit (Limit of quantitation). A hazard quotient greater than one (HQ >1) indicates that there is no margin of safety and there is a risk to human health that warrants further investigation. A hazard quotient less than one (HQ < 1) indicates that the groundwater level of APIs is less than the ADE and no appreciable human health risk exists.

6.3 Results

6.3.1 ADEs

ADEs were calculated for 29 APIs. Based on available preclinical data, none of the APIs are considered mutagenic carcinogens. The rationale for applying UFs for the derivation of ADE is shown on Table 6.1 and the basis for selecting the PODs is summarized in Table 6.2. The combined uncertainty factors (UFC) ranged from 15 (for amitriptyline and ketotifen) to 1350 (for trimethoprim). The ADEs derived for APIs ranged from 0.13 mg/day (for norethisterone and ketotifen) to 11mg/day (for metformin). For many APIs, the POD was established from the lowest therapeutic dose level (TDL) administered during clinical trials and/or post marketing surveillance.

For many APIs, more than one critical effect (i.e. treatment emergent adverse effect) was reported at the administered TDL and in such cases, consideration was given to the most common adverse effects (i.e. higher incidence rate; >1%) reported at the lowest administered TDL. In some cases, adjustments for sensitive or susceptible subpopulations were factored into ADE derivation by establishing a POD from a low clinical dose or LOAEL in the sensitive subpopulation or by accounting for additional variability or severity of effects in the modifying factor. In some cases, the POD was based on toxicological effects reported in nonclinical studies and the dose was adjusted downward to account for various uncertainties associated with extrapolation from animal data.

Table 6. 2 Estimated ADE for 29 APIs, critical effects and basis for POD

Substance	Therapeutic class	UF_H	UF_A	UF_L	UF_s	UF_D	MF	UF_C	ADE (mg/day)	Critical effect and basis for POD
Amitriptyline	Antidepressant	5	1	3	1	1	1	15	1.3	**Gastrointestinal/Cardiovascular effects** (LOAEL, based on lowest therapeutic dose of 20mg/day in divided doses being the low end of the recommended dose range for the treatment of depression in a very sensitive population (i.e. elderly or debilitated patients) (Teva, 2016)
Artemisinin	Antimalarial agent	10	1	3	1	3	3	270	0.93	**Neurotoxic/Cytotoxic effect**. (LOAEL, lowest oral starting dose of 250mg/day for a surrogate chemical (artesunate) for the treatment of uncomplicated malaria infections in adults (Medhi, Patyar, Rao, Ds, & Prakash, 2009)
Atenolol	Anti-hypertensive	10	1	3	1	1	3	90	0.56	**Hepatic system effect** (Elevated liver enzymes) (LOAEL, lowest starting dose of 50mg/day for the treatment of hypertension in adults; and lowest dose tested in a post marketing experience (AstraZeneca Pharmaceuticals, 2011).
Caffeine	Stimulant	10	1	3	1	1	1	30	0.50	**Therapeutic effect.** POD is the lowest therapeutic dose level of 15mg/day being the low end of the recommended dosing range in cold and allergy relief formulations (IARC monograph, Volume 51)
Carbamazepine	Anticonvulsant	10	1	10	3	3	1	900	0.44	**Critical effects**: in various human studies effects include hematologic effects (decreased white blood cell counts; aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, hepatitis, jaundice); Kidney effects (antidiuresis); reproductive endocrine effects (male/female sex hormone disturbances) POD is the LOAEL based on minimum therapeutic dose for adults at 400 mg/day (200 mg 2x/day) for the treatment of epilepsy (Minnesota Department of Health, 2013).

Table 6.2 (Continued)

Substance	Therapeutic class	UF_H	UF_A	UF_L	UF_s	UF_D	MF	UF_C	ADE (mg/day)	Critical effect and basis for POD
Cetirizine	Antihistamine	10	1	3	1	1	1	30	0.17	**Critical effect (s).** In pediatric clinical trial, adverse reaction profile in children shows effects on Nervous (headache, somnolence) and Gastrointestinal systems (abdominal pain; nausea). POD is the LOAEL, based on administered pediatric dose of 5 mg/day (McNeil Consumer Healthcare, 2017)
Cimetidine	Histamine H2 inhibitor	10	1	3	1	1	1	30	13	**Therapeutic effect**. POD is based on the lowest single therapeutic dose of 400 mg/day for prophylaxis of recurrent duodenal or gastric ulcer (TEVA Canada Limited, 2014)
Ciprofloxacin	Antibiotic	10	1	3	3	3	1	270	1.6	**Critical effect (s**). During clinical investigations and post marketing surveillance, drug related adverse reaction profile in adults shows effects on Gastrointestinal (nausea, diarrhea); Cardiovascular (palpitation; tachycardia); Nervous (tremor, palpitation, dizziness); respiratory system (dyspnea). POD is LOAEL; lowest therapeutic dose of 500mg/day for the treatment of mild to moderate Urinary Tract Infection (PRODOC LTEE, 2008)
Citalopram	Antidepressant	10	1	3	3	1	1	90	0.22	**Critical effects**. In a 6-week premarketing surveillance, adverse events in depressed patients shows effects on Central and Peripheral Nervous system (Tremor); Gastrointestinal system (nausea, diarrhea); Psychiatric (Somnolence); male Reproductive system (ejaculation disorder); POD is LOAEL based on the lowest recommended single oral dose of 20mg/day for the treatment of depression in adults (Lundbeck Canada Inc 2016).

Table 6.2 (Continued)

Substance	Therapeutic class	UF_H	UF_A	UF_L	UF_s	UF_D	MF	UF_C	ADE (mg/day)	Critical effect and basis for POD
Clarithromycin	Antibiotic	10	1	3	1	1	5	150	3.3	**Critical effects**: In human clinical trials, adverse events include Gastrointestinal effects (constipation, nausea, abdominal pain); Hepatobiliary disorder (Hepatitis, jaundice); Nervous System disorder (dizziness, somnolence, convulsion). POD is lowest therapeutic dose level (TDL) of 500 mg/day (250mg 2x/day) for the treatment of respiratory tract infection in adult
Desvenlafaxine	Antidepressant	10	1	3	3	1	1	90	0.56	**Critical effects.** In human study, treatment emergent adverse events include Gastrointestinal disorders (abdominal pain, constipation, diarrhea) and Nervous system disorders (dizziness, sedation, headache). POD is the LOAEL, based on the lowest dose of 50mg/day tested in a short-term clinical trial (Pfizer Canada Inc, 2018)
Diazepam	Anxiolytic	10	1	3	1	1	1	30	0.13	**Critical effects.** Post market adverse drug events include Digestive system effects (jaundice); Central Nervous System effects (drowsiness; fatigue). POD is LOAEL; based on the lowest recommended initial dose of 4mg/day (2mg 2x/day) for the symptomatic relief of anxiety and tension in psychoneurosis and anxiety reaction (Hoffmann-La Roche Ltd., 2018)
Diltiazem	Antianginal; Anti-hypertensive	10	1	3	1	1	3	90	2.0	**Cardiovascular effect** (Bradycardia). POD is LOAEL, based on diltiazem Extended-Release administered dose of 180mg/day for angina clinical study (Valeant Canada LP, 2017)
Fexofenadine	Antihistamine	10	1	3	3	1	1	90	1.3	**Gastrointestinal effect** (nausea). POD is the LOAEL, based on twice daily dosing with 60mg (120mg/day) fexofenadine for seasonal allergic rhinitis clinical trials (Aventis Pharmaceuticals Inc., no date)

Table 6.2 (Continued)

Substance	Therapeutic class	UF_H	UF_A	UF_L	UF_s	UF_D	MF	UF_C	ADE (mg/day)	Critical effect and basis for POD
Gabapentin	Anticonvulsant	10	1	3	1	1	5	150	4.0	**Critical effect(s).** In human clinical trials, treatment-emergent adverse event includes Nervous system effect (somnolence, ataxia); Respiratory effect (Rhinitis); Cardiovascular (hypertension); Digestive (anorexia); Respiratory (pneumonia). POD is LOAEL, based on 600 mg/day dosing in patients with partial seizures in a clinical trial of 12-week duration (Gen Med, 2006)
Hydrocodone	Analgesic /Antitussive	10	2	1	3	1	1	60	4.4	**Animal study NOAEL**. POD is the NOAEL based on oral maternal toxicity study established at a dose of 5.3 mg/kg in rabbits [Weight adjustment =50kg] (TOXNET)
Ketotifen	Antihistamine	5	1	3	1	1	1	15	0.13	**Critical effects**. Pediatric clinical trial adverse drug events include Central Nervous System effect (Sedation) and Gastrointestinal effect (abdominal pain; weight gain). POD is the LOAEL, lowest effective daily oral dose of 2 mg in divided doses recommended for the treatment of asthmatic conditions in sensitive subpopulation (children older than 3 years of age) (Teva Canada Limited, 2010)
Metformin	Hypoglycemic agent	10	1	3	3	1	1	90	11	**Gastrointestinal effect** (s) POD is the LOAEL based on minimum starting dose of 1000mg/day, and lowest dose tested in a 24-week clinical trial (Valeant Canada LP).
Metronidazole	Antibiotic	10	4	1	3	1	3	360	10	**Animal study NOAEL**. POD is the NOAEL based on the 80-week oral rat tumorigenicity study established at a dose of 75 mg/kg-day. [Weight adjustment =50kg].
Naproxen	Anti-inflammatory	10	1	3	3	1	1	90	2.4	**Critical effects**. In human clinical trials adverse events include Gastrointestinal (constipation, heartburn, abdominal pain); Central Nervous System (fatigue); Dermatologic (skin eruptions); Cardiovascular (palpitations). POD is the LOAEL, based on lowest recommended effective dose of 220 mg for the relief of mild to moderate pain in adult (Martindale, 2011).

Table 6.2 (Continued)

Substance	Therapeutic class	UF_H	UF_A	UF_L	UF_s	UF_D	MF	UF_C	ADE (mg/day)	Critical effect and basis for POD
Oseltamivir	Antiviral	10	1	3	1	1	1	30	2.5	**Gastrointestinal effect**. POD is the LOAEL, based on lowest recommended oral dose of 75mg once daily in adult for prevention of influenza (Hoffmann-La Roche Limited, 2017)
Paracetamol	Analgesic	10	1	3	3	3	1	270	7.2	**Increased serum liver enzymes in humans**. POD is LOAEL based on dosing of 1950 mg/day (Minnesota Department of Health, 2015).
Propranolol	Anti-hypertensive	10	1	3	1	1	1	30	1.0	**Gastrointestinal effect**. POD is the LOAEL, based on the low end of the starting dose range of 30mg/day (10mg in three divided doses) lowest effective therapeutic dose of 30 mg/day (taken in three divided doses). (Teva Canada Limited, 2011).
Ranitidine	Antihistamine	10	1	3	1	1	1	30	5.0	**Critical effects**. In human critical trials or in the routine management of patients treated with ranitidine, adverse events include Central Nervous System (somnolence); Cardiovascular (tachycardia, bradycardia); **Gastrointestinal** (constipation, diarrhea, nausea). POD is the LOAEL based on the recommended oral daily dose of 150mg/day in adults for chronic maintenance therapy in patients with recurrent ulcer (GlaxoSmithKline, 2015).
Sulfamethoxazole	Antibiotic	1	1	10	10	2	1	200	6.2	**Animal study NOEL**. POD is based on NOEL for thyroid tumors in rats. The human relevance of this finding is unknown (Schwab et al., 2005)[Weight adjustment = 50kg].
Tramadol	Opiate analgesic	10	1	3	1	1	1	30	3.3	**Gastrointestinal effect**. POD is the LOAEL, based on the lowest starting dose of 100mg/kg-d recommended for the management of moderately severe pain in adults (Paladin Labs Inc., 2018)

Table 6.2 (Continued)

Substance	Therapeutic class	UF_H	UF_A	UF_L	UF_s	UF_D	MF	UF_C	ADE (mg/day)	Critical effect and basis for POD
Trimethoprim	Antibiotic	5	1.8	10	3	1	5	1350	0.89	**Animal study NOEL**. POD is the NOEL of 20mg/kg/day for treatment-related gastrointestinal tract effects in dogs (Arcelin, 2013). [Weight Adjustment=60 kg]
Venlafaxine	Antidepressant	10	1	3	3	1	5	450	0.083	**Critical effects(s).** Cardiovascular system (neuroendocrine mediated increase in blood pressure); Developmental (persistent pulmonary hypertension in newborns); Gastrointestinal system (constipation); Male reproductive effects (ejaculation failure). POD is the LOAEL; based on the lowest starting dose of 37.5 mg/day; and lowest dose tested in a 6-month clinical trial (MDH, 2011)
Verapamil	Anti-arrhythmia agent	10	1	3	1	1	1	30	3.3	**Critical effect(s**). In clinical trials or marketing experience adverse events include vascular (hypotension) and cardiac (Edema, bradycardia) disorders. POD is the LOAEL, based on lowest recommended daily oral dose of 100 mg for the treatment of hypertension in a sensitive subpopulation (i.e. geriatric population)

6.3.2 Risk characterization

Nearly half of APIs evaluated in this study were detected at levels above the LOQ in drinking water and the highest MEC (MEC_{max}) of APIs reported in groundwater varied widely and ranged from 1.9 ng/L (for ketotifen) to 1250 ng/L (for sulfamethoxazole) (Figure 6.1). For 16 APIs, concentrations in groundwater were typically less than 100 ng/L.

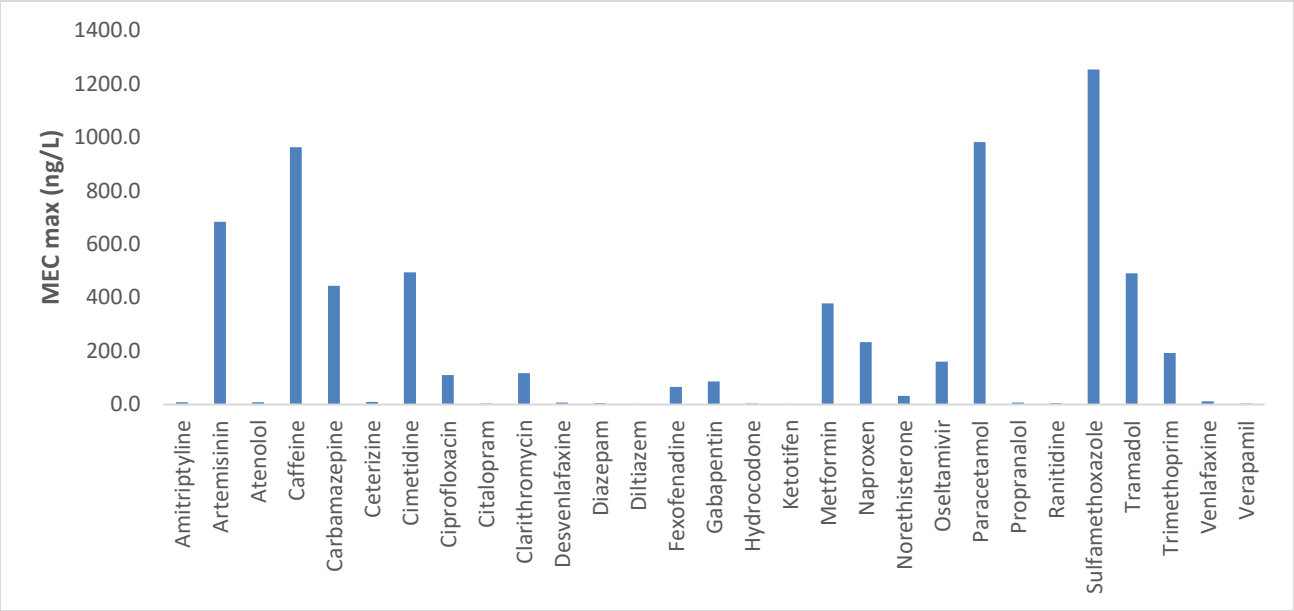


Figure 6. 1 Highest measured concentrations of APIs in groundwater in unsewered communities

The Exposure / ADE ratio (HQ) derived from the highest measured groundwater concentrations are depicted in Figure 6.2. For all APIs, HQs were considerably less than 1 and ranged from 1.5 x 10^{-6} for hydrocodone (opioid narcotic) to 0.0039 for caffeine (stimulant).

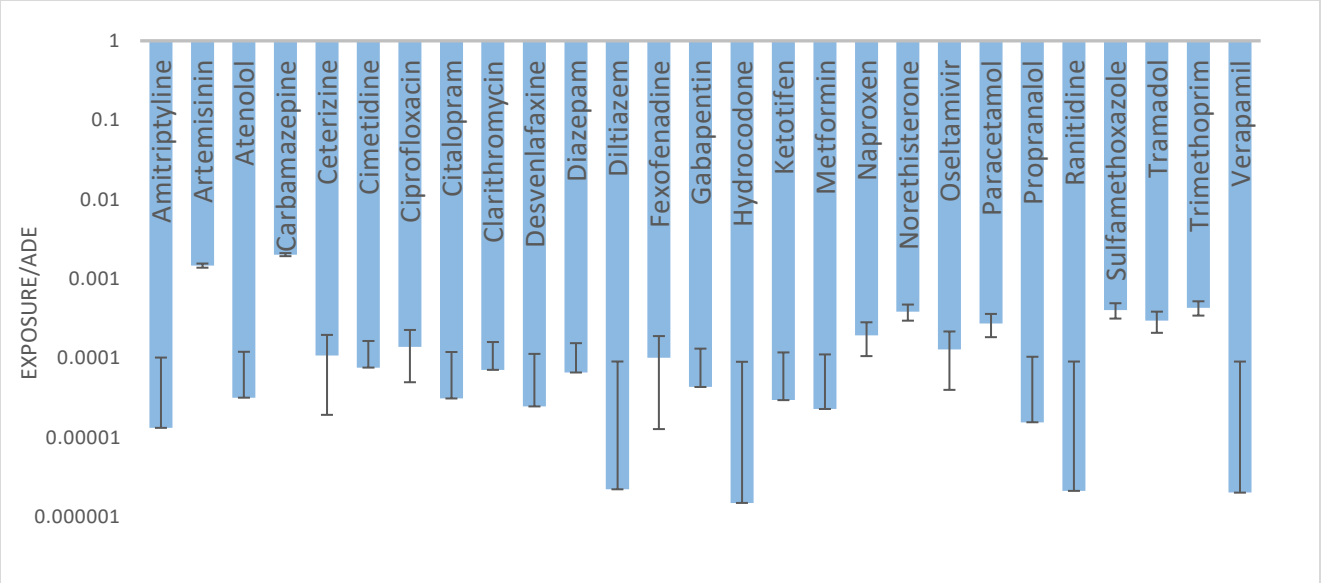


Figure 6. 2 Hazard quotient for APIs in drinking water

6.4 Discussion

Twenty-nine APIs evaluated in this study represent a broad range of API classes including antidepressants, antimalarials, antihypertensives, anticonvulsants, antihistamines, antibiotics, analgesics and contraceptives. Sixteen out of 29 APIs were detected at levels above the LOQ in drinking water. By comparing the highest MEC in drinking water supply to ADEs derived for drinking water, this method assumes maximum potential exposure. The main finding of this study was that measured levels of APIs in drinking water supply do not pose appreciable risk to human health and HQ values (Figure 6.2) show a considerable margin of safety suggestive of low-level exposure to APIs in drinking water. The methodology utilized in the derivation of ADEs is holistic and consistent (Table 6.1). While previous methods for the establishment of acceptable limits for chemicals are often based on the use of arbitrary values, the derivation of ADEs as a health-based limit follows a systematic approach, which emphasizes the use of available toxicological and pharmacological data (including clinical data) for individual APIs (Sargent et al., 2013). Thus, by considering both clinical and nonclinical data for individual APIs, and by applying appropriate

uncertainty and modifying factors to the selected starting dose (POD), as recommended in various guidance documents on the establishment of health based limits, it is assumed that the ADEs derived in this study represent a 'safe' dose that will protect the general population (including sensitive subpopulation) from potential adverse health effects associated with nontherapeutic exposure to APIs in drinking water over a lifetime. Furthermore, the consideration of 'critical effects' and the selection of subpopulation specific therapeutic dose as a starting dose in the derivation of ADEs are ultimately protective, given that protection against the critical effects, triggered at the lowest dose, invariably protects against all other adverse effects (Meek et al., 2002).

The finding of no adverse effect to human health from exposure to trace quantities of APIs in drinking water supply in this study agrees with previous investigations. Houtman et al. (2014) assessed the lifelong exposure of consumers to pharmaceuticals through Dutch drinking water and the possible health risk associated with this exposure and determined that lifelong exposure to and risk of adverse effects from pharmaceuticals in drinking water were negligible. In German drinking water, Webb et al. (2003) reported no substantial concerns with regard to indirect exposure to 64 pharmaceuticals in drinking water. Assessment of health risks related to the presence of drug residues found that exposure to carbamazepine and its major metabolite through drinking water is likely to be of negligible risk to human health (Mauclaire et al., 2011). Schulman et al. (2002) utilized detailed toxicological and pharmacological parameters to assess the potential risk from chronic exposure to four pharmaceuticals of varied therapeutic classes in surface water and drinking water and found no appreciable risk to humans.

Although for many APIs, the potential exists for additive, antagonistic or synergistic drug interactions, this assessment was carried out as a chemical specific risk assessment, which requires the evaluation of APIs individually; hence, it does not account for the potential impact on human health of exposure to API mixtures.

As ADEs are widely used for cleaning validation purposes and for evaluating cross-contamination to support risk-based manufacturing of pharmaceutical products (Sargent et al., 2013), this study is one of the first few attempts at utilizing ADEs as a health-based limit for human health risk assessment of APIs as contaminants in drinking water. It is important therefore, to mention that variations are bound to occur across derived ADEs due to the considerable use of expert judgement in the selection of PODs and in the application of adjustment and modifying factors. Some of the decisions made may be based on subjective perception of risk and such the findings must be interpreted with caution in view of the current scenario of use and the subjective nature of the selection of various parameters utilized in the assessment of risk. Furthermore, given that HQ was established for only one age group (i.e. adults), the risk of nontherapeutic exposures to APIs may have been overlooked for infants and toddlers who may have lower margin of safety than adults and as such requires further assessment.

6.5 Conclusion

The occurrence of APIs in drinking water supplies is an indication of potential indirect human exposure to APIs through drinking water intake. There is concern over public health safety regarding non-therapeutic exposure to APIs. ADEs have been employed to evaluate the significance of such indirect exposure in an area where water treatment utilities are limited. Potential human health risk from pharmaceutical exposure through drinking water intake has been assessed by benchmarking maximum measured environmental concentrations from groundwater monitoring data against acceptable daily exposure limits (ADEs). For all APIs assessed the risk of adverse effects appeared to be negligible. While there are some reservations concerning the considerable use of scientific/expert judgement for the derivation of ADEs due to the potential subjectivity in the perception of risk, this approach provides a holistic and consistent framework for the evaluation of indirect exposure to APIs in drinking water. However, despite the provisional indications that risk is likely to be low, the need for periodic groundwater monitoring cannot be

ignored and some consideration will always be required regarding chronic low-level human exposure to APIs, their metabolites and degradation products and the potential for adverse interaction of API mixtures in drinking water.

Chapter 7

General discussion and Conclusion

7.1 Introduction

In the last two decades, the focus of environmental research has extended beyond conventional environmental pollutants (such as pesticides, POPs) to PPCPs released into the environment following regular household use (aus der Beek et al., 2016). The growing interest in PPCPs is prompted by their ubiquitous presence in the environment, their bioactive characteristics and the potential for mixture toxicity even at trace concentrations. Wastewater treatment systems, in general, are not designed to adequately remove PPCPs from wastewater, and consequently, these systems have become a significant pathway for the release of PPCPs into the environment (Boxall et al., 2012). The majority of PPCP research has been focused on developed countries notably Europe, United Kingdom and North America (aus der Beek et al., 2016) with extensive lack of knowledge about environmental exposures to PPCPs in other parts of the world particularly the African region (Hughes et al., 2012). In addition, studies on the impact of wastewater treatment on the environment has been conducted more extensively in WWTPs and receiving surface waters (Ternes, 1998; Garcia et al., 2013; Baker & Kasprzyk-Hordern, 2013; Margot et al., 2015) than in septic systems and receiving aquifers (Du et al., 2014; Conn et al., 2006; Barnes et al., 2008) even though the global reliance on septic systems has increased over the last decade (Conn et al., 2006). The aim of the work presented in this thesis was therefore to characterize the occurrence and concentrations of PPCPs in groundwater affected by septic systems and assess the potential human health risk of indirect exposure to APIs in drinking water. This chapter summarizes the findings and implications of the different components of the thesis. The recommendations for future research based on each data chapter are highlighted.

7.2 Summary and Implications of Findings

The research in this PhD commenced with an extensive review of the literature to determine the impact of septic systems on the underlying aquifer and adjacent drinking water wells regarding emerging organic contaminants (EOCs). This review highlighted the widespread contamination of groundwater by a variety of EOCs including PPCPs, industrial compounds, lifestyle compounds and food additives, which migrate from septic systems to the underlying aquifers. It is interesting to note that the dominant group of API classes (e.g. antibiotics, antiepileptics and anti-inflammatory drugs) often associated with wastewater treatment processes (Drewes et al., 2002; Monteiro and Boxall, 2010) were also the most frequently reported APIs in onsite wastewater and groundwater downgradient of septic systems across the literature. As expected, concentrations of EOCs were much lower in groundwater samples compared with levels in onsite wastewater, suggesting potential for attenuation during subsurface transport (Verstraeten et al., 2005) and also the dilution potential of groundwater (Nielsen, 2016). The two most widely reported antibiotics in both onsite wastewater and groundwater were sulfamethoxazole and trimethoprim, which is not surprising as they are a combination antibiotic used to treat a wide range of infections. Sulfamethoxazole and trimethoprim were also among the most frequently detected compounds in groundwater in the current study. Although septic systems are used globally for sewage treatment in areas without sewer connectivity, all the studies reviewed were carried out in the United States and Canada, which supports the claim that septic systems and associated groundwater are understudied, particularly in developing countries where these systems are prevalent. This is the first study that has been conducted to characterize PPCP occurrence in groundwater affected by septic systems in southern Nigeria. This study provides a foundational list of APIs for future groundwater monitoring programs in Nigeria and it is anticipated that this study will shape the direction and priorities for future research in API occurrence, fate and risks in Nigeria and other countries in Africa

Use and disposal pattern of consumer products such as PPCPs have been highlighted as one of the factors that would determine the composition of wastewater and the types and quantities of chemical emissions reaching the local environment (Teng et al., 2012), and which may be imperative to establishing realistic exposure estimates (Price et al., 2010; Biesterbos et al., 2013), and monitoring protocols (Kookana et al. 2014.; Franco et al. 2016) for risk assessment. However, such information is hardly available in low to middle income countries and the low research output in many developing countries has been linked partly to the paucity of such relevant data. In the second phase of this research, survey of household use of PPCPs was conducted to estimate the annual consumption mass of APIs per capita and annual household consumption of PCPs, to determine the dominant routes of disposal of unwanted PPCPs and elicit WTP for groundwater protection program. Although using survey to estimate API usage is not a typical approach, Kostich et al. (2010) suggest that in the absence of country-wide consumption data, surveys of API dispensing can be used as a proxy. The survey results involving 350 participants in southern Nigeria revealed that paracetamol (an analgesic) was consumed in the highest amount (92.7 g per capita per year) and the API with the lowest annual per capita use was triprolidine (nasal decongestant). The result is consistent with previous findings of extensive global use of paracetamol (Hamunen et al., 2008), and country-wide use in Croatia (Krnic et al., 2015), Australia, China, Malaysia, Canada (Krnic et al., 2015) and Lebanon (Massoud et al., 2016). Another notable result from this survey was that participants reported relatively higher days of therapy for artemether / lumefantrine (DOT = 3872) compared with chloroquine (DOT = 308) and quinine (DOT = 772). This may be attributed to the current switch from the use of monotherapy to artemisinin-based combination therapies recommended by WHO for the treatment of uncomplicated malaria in endemic regions. Participants also reported the use of a wide range of antibiotics (e.g. ampicillin, tetracycline, ciprofloxacin, cloxacillin, sulfamethoxazole and trimethoprim) and estimated annual per capita use ranged from 0.66 g (trimethoprim) to 18.0 g (ampicillin). This may reflect the easy accessibility to antibiotics, which are often obtained over-

the-counter in Nigeria and in many other developing countries. Although, the range of medicines consumed by participants are in the list of essential medicines (World Health Organization, 2015a), about 45% (n = 158) of participants reported that they often obtained medications without prescription.

Regarding PCP usage, 54 assorted compounds were used in households and it was estimated that each household consumed approximately 61 litres of PCPs per year with cleaning products accounting for over 47% of this volume. Household pesticides were the most dominant PCPs with an estimated average annual use of 9.6 litres per household. High household pesticide use is not surprising, as it is widely used in the control of pests, particularly mosquitoes in Nigeria and in other malaria endemic regions. Among the 25 identified active ingredients in the various household consumer products, surfactants were the most consumed (4.7 litres), likely because surfactants are contained in several household products. Consistent with the wider literature (Daughton and Ruhoy, 2009; Ekedahl, 2006; Braund et al., 2009), PPCP disposal was mainly by trash, with over 80% of households discarding unwanted medicines and PCPs with household waste. There is currently no medicine take-back program in Nigeria, but over 90% of participants would be willing to take back unused medications to the pharmacy if such a program was implemented. Over 60% of participants are willing to pay a fee for groundwater protection program, but fee amount was statistically correlated with gender, income and education completed, with educated men with higher income less likely to pay lower fees.

PPCPs identified in the survey are likely to be emitted into the environment primarily through onsite wastewater treatment and disposal systems. A risk-based prioritization model which used a combination of exposure and effects measures was then developed to prioritize APIs and PCP active ingredients (AIs) with the greatest potential to migrate from septic systems to groundwater used as a source of drinking water. The results indicate that 14 APIs and 9 PCP active ingredients had risk index (RI) exceeding 0.01, suggesting that these compounds are high priority compounds

for future groundwater monitoring in southern Nigeria. Among the top 14 ranked APIs (ciprofloxacin, trimethoprim, ampicillin, tetracycline, sulfamethoxazole, cloxacillin, acetaminophen, pseudoephedrine, metamizole, guaifenesin, diphenhydramine, artesunate, artemether and dextromethorphan), the majority are antibiotics, four of which (ciprofloxacin, ampicillin, tetracycline and trimethoprim) have been associated with the occurrence of resistant strains of bacteria in water and sediment samples from Canada (Maal-Bared et al., 2013). Interestingly, many of the top-ranking APIs and PCP AIs in this study were also observed as compounds of top priority in other countries (Dong et al., 2013; Perazzolo et al., 2010; Guo et al., 2016; Burns et al., 2018). Regarding PCP AIs, the most relevant in terms of their potential to enter groundwater include dichlorvos (organophosphate insecticide), sodium carbonate (water softener), ammonium thioglycolate (perm salt), cetrimide (antiseptic), cresol (antibacterial agent), chlorhexidine (disinfectant) and surfactants. Dichlorvos, the compound with the highest RI in this study, is highly soluble in water (18000mg/L) and has a low soil adsorption coefficient (log K_{oc} = 1.4), which indicates its predominance in the aqueous phase and a great potential for mobility in soils (Mccall et al., 1980). Its top RI value in this study reflects its high usage. Other high ranking PCP AIs in this study, notably biocides (disinfectants and surfactants), are recognized as resistant-driving chemicals, with the potential to select for resistant genes in the environment (European Commission, 2009).

After developing a priority list of contaminants for the study area, robust and sensitive analytical methods were developed to characterize the occurrence and concentrations of PPCPs in domestic water wells down gradient of septic systems in southern Nigeria. APIs in groundwater were analyzed by a novel method developed for the simultaneous analysis of 61 APIs and metabolites (Wilkinson et al., 2019) using HPLC-MS/MS. Dichlorvos, was determined using GC-MS after solid phase extraction. More than half (64%, n=39) of the 61 target APIs were detected in groundwater samples and they comprised a wide range of therapeutic classes, including anti-

depressants, antimalarials, antihypertensives, stimulants, anticonvulsants, antihistamines, antibiotics, antifungals, antianginals, anxiolytics, anti-inflammatory, antivirals, analgesics and anti-asthmatics. All the 53 sampled wells contained detectable levels of at least two APIs with highly variable concentrations among the detected compounds (1.93 ng/L for ketotifen and 1250 ng/L for sulfamethoxazole). The five most frequently detected compounds include trimethoprim (antibiotic, 77%), sulfamethoxazole (antibiotic, 72%), naproxen (anti-inflammatory, 64%), caffeine (stimulant, 62%) and paracetamol (analgesic, 60%); interestingly, these compounds were among the most frequently detected compounds in groundwater sites affected by septic systems in the United States and Canada (Carrara et al., 2008; Schaider et al., 2014; 2016; Hinkle et al., 2005; Verstraeten et al., 2005; Godfrey et al., 2007; Phillips et al., 2015; Katz et al., 2010; Dougherty et al., 2010). The high detection frequency of target compounds in domestic water wells demonstrates that effluent from septic systems is a significant source of APIs to groundwater and this finding is consistent with existing research which reports the ubiquitous nature of pharmaceuticals in wastewater receiving environments, particularly in groundwater and surface water (Heberer, 2002).

Mixtures were common, with 2 or more APIs detected in all the sampled wells and 5 or more APIs detected in 45 (85%) of the 53 sampled wells. The number of API detections in groundwater samples ranged from 7 to 22 detections in the shallower wells from Enugu Metropolitan Area and 2 to 15 detections in the deeper wells from Port Harcourt Metropolitan Area. Earlier studies have also reported significantly higher detection of pharmaceuticals in shallower wells (Barnes et al.,2008) and lower detections in deeper wells (Fram and Belitz, 2011). When compared with previous studies, notable differences were observed in the levels of APIs detected in groundwater samples. Maximum concentrations of nine pharmaceuticals detected in this study (e.g. atenolol (antihypertensive), carbamazepine (anticonvulsant), cimetidine (antihistamine), ciprofloxacin (antibiotic), cotinine (nicotine metabolite), paracetamol (analgesic) and tramadol (opioid

analgesic) exceeded the maximum concentrations reported in previous studies (Schaider et al., 2014; 2016; Godfrey et al. 2007; Hinkle et al., 2005; Verstraeten et al., 2005; Phillips et al., 2015; Katz et al., 2010; Dougherty et al. 2010). Twenty-two pharmaceutical compounds were not detected in groundwater samples in this study; the less frequently detected APIs (<3%) include salbutamol, fluoxetine and norfluoxetine. Artemisinin, an antimalarial agent was detected in 5% of the sampled wells in this study and has not been reported in previous studies. Although antibiotics were the dominant class of APIs detected in the current study, the maximum measured environmental concentrations in groundwater samples for six antibiotics (ciprofloxacin, clarithromycin, erythromycin, metronidazole, sulfamethoxazole and trimethoprim) did not exceed the predicted no effect concentration for resistance selection (Bengtsson-Palme & Larsson, 2016) suggesting that their presence in groundwater does not pose any risk of resistance promotion.

Dichlorvos was detected in 12 out of 20 sampled wells at concentrations ranging from 1.88 ng/L to 68.0 ng/L, which are below the EU drinking water maximum allowable concentration of 0.1 µg/L for pesticides (European Commission, 1980). The presence of dichlorvos in groundwater samples may be attributed to its intensive use in Nigerian households as it is the active ingredient widely used in locally formulated insecticides for the control of household pests in many Nigeria households (Kanu et al., 2016) and for the protection of stored products from insects by farmers and traders.

Although it is generally expected that shallow domestic wells in close proximity to septic system leach fields or seepage pits would have a higher pollution risk as they would be more susceptible to contamination by septic system leachates (Bremer and Harter, 2012; Schaider et al., 2011), in this study, there was a weak correlation between well depth and the number of detections of APIs (i.e. pollution risk) and there was no relationship between the number of API detections and setback distance. Regression analysis shows that the relationship between well depth and number of detections is statistically significant ($p<0.05$) but based on the R-squared value (which

indicates how much of the variability in the number of detections is explained by well depth), only 15 percent of the variability in the number of detections can be explained by well depth; there was no statistically significant relationship ($p>0.05$) between setback back distance and the number of detections, which means that the number of target compounds in wells does not correlate to setback distance. This suggests that well depth and setback distance do not explain much of the variability in the number of detections across sampled wells, and that other drivers of wastewater impact such as septic system density is likely influencing the vulnerability of groundwater to septic system leachates. Several septic system density related studies have reported a strong correlation between septic system density and the number and concentrations of contaminants in sampled wells (Standley et al., 2008; Whitehead and Geary, 2000). Given that in this study, wells in closely built up areas (i.e. high spatial septic system density) were prioritized for sampling, it is reasonable to assume that the excessive septic system density (6 to 8 septic systems per acre of land) in the study area may have contributed substantially to the number and concentrations of the target compounds observed in the sampled wells.

Given the high frequency of occurrence of APIs in groundwater samples from southern Nigeria, the possible health risks associated with indirect exposure to APIs in untreated water was assessed by benchmarking exposure (highest maximum detected concentrations (MECmax) in groundwater with derived exposure limits (ADEs). The ADEs represent a substance specific dose that is unlikely to cause any adverse health risk if an individual is exposed, by any route at or below this dose every day for a lifetime (EMA, 2014). Thus, the derivation of ADEs for APIs as a potential contaminant in drinking water aims to reduce API exposure to a dose that has no adverse health effects to the potentially exposed population, including healthy adults, as wells susceptible subpopulations (e.g. children, the elderly and gravely ill individuals) (Sussman et al., 2016). The Exposure / ADE ratio (HQ) derived from MECmax were considerably less than 1 and ranged from 1.5×10^{-6} for hydrocodone (opioid narcotic) to 0.0039 for caffeine (stimulant). This suggests that

APIs in groundwater used for drinking do not pose an appreciable risk to human health and that there is a considerable margin of safety (up to two orders of magnitude). It needs to be said however, that HQs were determined for one age group (adults). Thus, the risk of nontherapeutic exposures to APIs in drinking water may have been overlooked for infants and toddlers who may have lower margin of safety than adults (Bercu et al.,2008) and as such requires further assessment.

7.3 Recommendations and Future Work

The work performed in this thesis provides novel information on the occurrence and concentrations of PPCPs in drinking water supplies in non-sewered communities in southern Nigeria. Below we provide recommendations for future work that are needed to build on the findings of this thesis.

1). The use of survey as a proxy to estimate PPCP consumption data – The main restraint in the use of survey as a surrogate to country-wide consumption data for APIs is recall issue. Because respondents were asked to recall their use of PPCPs during the previous year, there is always a potential for distortion caused by recall bias whenever information of past experiences are elicited. This makes it difficult to ascertain whether respondents were systematically underreporting or overreporting use. This may have placed a lot of uncertainties around the estimates of product use. The use of survey for this purpose has not been widely applied and when validated against monitoring data, the presence of more compounds in the sampled wells (Chapter 5) than were reported in the survey confirms that usage was underestimated by participants. Therefore, it is recommended that survey data be used in combination with other sources of data (such as hospital data) where available, to minimize the potential for recall bias and to provide estimates that mirror actual usage.

2). Many participants (45%, n = 158) reported that medicines were often obtained without prescriptions and this may lead to the potential for abuse of medicines. This calls for the need to set quantitative targets for rational drug use through a national action plan and to promote rational use by raising knowledge and awareness levels of physicians, pharmacists, allied health personnel and the public, as currently practiced in many countries such as Turkey. It is recommended that increased awareness of medicine dispensing, and consumption behaviour be raised among healthcare professionals and that medicine use patterns be regulated across Nigerian communities, through the development and enforcement of rational use policies. Enforcing legislations that will restrict over the counter sale of medicines like antibiotics would be a good starting point, as self-medication is widely practised in the study area.

3). The predominant route of PPCP disposal in many Nigerian households is by trash. Under this current disposal scenario, there is little scope for reductions in the input of pharmaceuticals to landfills since disposal to trash would remain the most viable option available to households as there is no medicine takeback program. In this regard, there may be need to embrace other strategies such as the 'upstream green approach' with even greater potential to lessen the accumulation of leftover medications and the subsequent need of disposal.

4). Risk-based prioritization approach –The PPCP dataset considered in this study was based on 2016 household usage survey data of 350 respondents, a source which may likely provide a less accurate estimation of PPCP usage mass, which is an important exposure parameter in the prioritization model. As, mentioned above, survey estimates should be used in combination with other sources of data (such as marketing data) if available. Another constraint is the uncertainty regarding the accuracy of model estimates which were used as substitutes for non-existing experimental data (such as degradation rates) for several compounds during prioritization. For this reason, it is recommended that estimated values be used only on a screening level (i.e. to determine occurrence for monitoring purposes other than regulatory purposes).

5) Various API classes including antibiotics, analgesics, antimalarial agents, antihistamines, suppressants and decongestants and various classes of PCP active ingredients including organophosphate insecticides, biocides and surfactants have been identified as high priority classes of chemicals in terms of their potential to be available in groundwater. It is recommended that future groundwater monitoring campaigns should be guided by the prioritized list to ascertain the presence of these compounds in groundwater and characterize the nature of any potential risk.

6).Transformation products have not been considered during the prioritization exercise even though it is known that APIs can be metabolized after use, or if excreted intact, can degrade in the environmental media resulting in metabolites and degradation products, which in some cases could be more potent than the parent compounds. PCPs can also degrade in the environment into more harmful transformation products. Hence, future prioritization exercises should consider transformation products as relevant data on these compounds become more readily available.

7). Monitoring of PPCPs (API and dichlorvos) in groundwater from unsewered communities has clearly shown the vulnerability of the underlying aquifer to septic system leachates. Mixtures were common, with 5 or more APIs detected in several samples, suggesting the potential for mixture toxicity. Given that the potential health effects of mixtures are uncertain, it is recommended that PPCP levels in groundwater systems be routinely monitored as a precautionary measure to their potential threats.

8). Shallow domestic wells, inadequate setback distance and high spatial septic system density are recognized as drivers of wastewater impact. Shallow wells close to septic system seepage pits had relatively more API detections than deeper wells. There are currently no guidelines for septic system design and operation in the study area and the improper management of septic systems may be contributing to septic system failure. In future, institutional capacity regulating

septic system use at the national, state and local levels are required to protect groundwater quality.

9). The spatial septic system density in many urban and suburban areas in Nigeria is 6 to 8 systems per acre of land. This is above the critical maximum density recommended in many studies. It is reasonable to assume that the excessive septic system density in the study area may have contributed substantially to the number and concentrations of the target compounds observed in the sampled wells. A septic system density study is required to predict reasonable septic system densities for the protection of groundwater quality in Nigeria.

10).The risk of potential adverse effects from indirect exposure to APIs was assessed by benchmarking exposure with derived acceptable daily exposure limits (ADEs) for individual APIs. Although Risk assessment results show that exposure to detected levels of single APIs in Nigerian groundwater currently do not pose an appreciable risk to human health, long term exposure to trace levels of chemical mixtures in drinking water may result in a relatively greater risk than that posed by individual substances due to potential for mixture toxicity and as such, underscores the need for further investigation. In addition, given that HQ was established for only one age group (i.e. adults), the risk of nontherapeutic exposures to APIs may have been overlooked for infants and toddlers who may have lower margin of safety than adults and as such requires further assessment.

Appendices

Appendix A

Table A.A1 Summary Data for Concentrations, Sampling Locations and Detection Frequencies for EOCs in Onsite Wastewater

Compound	Country / Sampling Location	RL	Concentration	Detection Frequency (%)	Reference
Pharmaceuticals					
Analgesics & anti-inflammatories					
Acetaminophen	USA- LaPine Oregon		E120µg/L		5
	USA- Montana		10^5ng/L		3
	USA- Montana		>1530µg/L	>60	4
	USA- Colorado		45µg/L		7
	USA- Woodville Florida	0.024µg/L	0.18-78.2µg/L	89	14
Diclofenac	Canada-Ontario	Na	Nd		1
	USA -Jefferson & Summit County, Colorado		<0.1µg/L		6
Ibuprofen	Canada		2400-6800ng/L		1
	USA-LaPine Oregon		<0.04µg/L		5
	USA- Jefferson & Summit County, Colorado		<0.1-E110µg/L		6
	USA-North Carolina		78.78µg/L	63	10
	USA-Colorado		5.1µg/L		11
	USA-Skaneateles New York	0.85ng/L	<RL-10,600ng/l		15
Ketoprofen	Canada-Ontario	Na	Nd		1
	USA - Jefferson & Summit County, Colorado		<0.1µg/L		6
			Nd		3
Naproxen	Canada-Ontario	Na	9-300ng/L		1
	USA - Jefferson & Summit County, Colorado		<0.1-E150µg/L		6
Salicylic acid	Canada Ontario		Nd-480ng/L		1
	USA - Jefferson & Summit County, Colorado		<0.1-210µg/L		6
Fenoprofen	Canada Ontario	Na	Nd		1
Indomethacin	Canada Ontario	Na	Nd-4 ng/L		1
Codeine	USA-La Pine Oregon		0.066µg/L		5
	USA-Montana		10^5ng/L		3
Hydrocodone	USA-Montana				3
Antipyrine	USA-Montana				3

Table A.A1 (Continued)

Compound	Country / Sampling Location	RL	Concentration	Detection Frequency (%)	Reference
Antibiotics					
Erythromycin	USA-Montana		Nd-18µg/L		3
	USA-Colorado		0.137µg/L		7
	USA- Colorado		0.02-0.04µg/L		11
Erythromycin-H2O	USA-Colorado		0.20-0.32µg/L		11
Sulfamethoxazole	USA-LaPine Oregon		<0.06µg/L		5
	USA-Montana		4200-29000ng/L		3
	USA- Montana		>64µg/L	<30	4
	USA-Woodville Florida	0.024µg/L	0.04µg/L	11	14
	USA-Skaneateles Lake New York	0.32ng/L	<0.32-37,700ng/L	68	15
Trimethoprim	USA-LaPine Oregon		0.19µg/L		5
	USA-Montana		10^5ng/L		3
	USA- Montana		>1.5µg/L	<30	4
	USA-Colorado		0.005-0.229µg/L		7
	USA- Colorado		0.01-0.07µg/L		11
	USA- Skaneateles Lake New York	0.37	<RL-4.77ng/L	11	15
Tetracycline	USA-Colorado		20µg/L		7
Ciprofloxacin	USA-Colorado		0.036-0.593µg/L		7
Norfloxacin	USA-Colorado		0.039-0.11µg/L		7
Ofloxacin	USA - Colorado		0.018-2.31µg/L		7
	USA -Colorado		0.45-0.96µg/L		11
Azithromycin	USA-Colorado		0.01-0.02µg/L		11
Beta-Blockers					
Atenolol	USA-Skaneateles	0.40ng/L	<RL-506ng/L	54	15
Lipid regulators					
Bezafibrate	Canada-Ontario	Na	Nd-12ng/L		1
Fenofibrate	Canada Ontario	Na	Nd		1
	USA-Montana		Nd		3
Clofibric acid	Canada-Ontario	Na	Nd		1
Gemfibrozil	Canada-Ontario	Na	15-620ng/L		1
	USA-LaPine Oregon		<0.01µg/L		5
	USA- Jefferson & Summit County, Colorado	0.1µg/L	<0.1µg/L		6
Antiepileptics					
Carbamazepine	USA-LaPine Oregon		<0.1µg/L		5
	USA-Montana		250-450ng/L		3
	USA- Montana		>6.4ng/L	<30	4
	USA-Colorado		0.0048µg/L		7
	USA-Skaneateles New York	0.03ng/L	<RL-2.04ng/L		15
β_2-sympathomimetics					
Salbutamol	USA-La Pine Oregon		<0.2µg/L		5
	USA Montana		Nd		3

Table A.A1 (Continued)

Compound	Country	RL	Concentration	Detection Frequency (%)	Reference
Steroid hormones					
Estrone(E1)	USA-Cape Cod		49-74ng/L		2
	USA-North Carolina		<0.4-260ng/L	65	13
	USA-Skaneateles New York	6.48ng/L	Nd-11.3ng/L	4	15
17β-estradiol(E2)	USA-Cape Cod		16-19ng/L		2
	USA-North Carolina		<1-84ng/L	53	13
	USA-Skaneateles New York	14.8ng/L	Nd-38.3ng/L	4	15
Estriol(E3)	USA-North Carolina		<2-380ng/L	36	13
17α-ethinyl estradiol (EE2)	USA-North Carolina		<2-36ng/L	19	13
	USA-Skaneateles New York	8.86ng/L	Nd-11.9ng/L	4	15
Coprostanol	USA-La Pine Oregon		<2-53µg/L	>90	5
	USA-Colorado		2800-7100[a c]µg/L	100	7
Cholesterol	USA-La Pine Oregon		<2-320µg/L	>90	5
	USA-Colorado		700-2200[a c]µg/L	100	7
Carbamazepine	USA-LaPine Oregon		<0.1µg/L		5
	USA-Montana		250-450ng/L		3
	USA -Montana		>6.4ng/L	<30	4
	USA-Colorado		0.0048µg/L		7
	USA-Skaneateles New York	0.03ng/L	<RL-2.04ng/L		15
Steroid hormones					
Estrone(E1)	USA-Cape Cod		49-74ng/L		2
	USA-North Carolina		<0.4-260ng/L	65	13
	USA-Skaneateles New York	6.48ng/L	Nd-11.3ng/L	4	15
17β-estradiol(E2)	USA-Cape Cod		16-19ng/L		2
	USA-North Carolina		<1-84ng/L	53	13
	USA-Skaneateles New York	14.8ng/L	Nd-38.3ng/L	4	15
H2 Blockers and Antihistamines					
Cimetidine	USA-La Pine Oregon		0.15µg/L		5
	USA-Montana		Nd		3
	USA-Colorado		0.28-12µg/L		7
Ranitidine	USA-La Pine Oregon		<0.01µg/L		5
	USA-Montana		10^5ng/L		3
Diphenhydramine	USA-La Pine Oregon		0.072µg/L		5
Calcium channel blockers					
Diltiazem	USA-La Pine Oregon		<0.02µg/L		5
	USA-Montana		Nd		3
Nifedipine	USA-Montana		Nd		3
Dehydronifedipine	USA-La Pine Oregon		<0.02µg/L		5

Table A.A1 (Continued)

Compound	Country / Sample Location	RL	Concentration	Detection Frequency (%)	Reference
Anti-coagulants					
Warfarin	USA-La Pine Oregon		<0.01µg/L	>50	5
	USA-Montana		10^5ng/L		3
	USA - Montana		>23µg/L	>77	4
Anthelmintic					
Thiabendazole	USA-La Pine Oregon		<0.01		5
Anxiolytics					
Fluoxetine (Prozac)	USA-Montana		Nd		3
Metformin	USA-Montana		Nd		3
Personal Care Products					
Insect repellant					
DEET	USA-La Pine Oregon		<0.5-52µg/L	>90	5
	USA-North Carolina		3.16[b]µg/L	88	10
Sunscreen agents					
Oxybenzone	USA-Skaneateles Lake New York	1.27ng/L	<RL-151ng/L	32	15
Homosalate	USA-North Carolina		4.49[b]µg/L	63	10
Antimicrobial					
Triclosan	Canada-Ontario		Nd-70µg/L		1
	USA - Jefferson & Summit County, Colorado		0.9-57µg/L		6
	USA-Colorado		9.3-82[a]µg/L	57-79	7
	USA- Colorado		5.0-14µg/L		11
	USA-Golden Colorado	0.2µg/L	5.0-14µg/L		12
	USA-Woodville Florida	1.0µg/L	<0.2µg/L		14
	USA-Skaneateles Lake New York	1.17ng/L	<RL-4640ng/L	36	15
Triclocarban	USA-Skaneateles Lake New York	0.70ng/L	<RL-270ng/L	79	15
Phenylphenol	USA-Cape Cod		1µg/L		8
Life Style Compounds					
Stimulants					
Nicotine	USA-Montana		10^5ng/L		3
Cotinine (Nicotine metabolite)	USA-LaPine Oregon		1.1µg/L		5
	USA-Montana		10^5ng/L		3
	USA-Colorado		0.92-3.9µg/L		7

Table A.A1 (Continued)

Compound	Country / Sample Location	RL	Concentration	Detection Frequency (%)	Reference
Life Style Compounds					
Stimulants					
Caffeine	USA-Cape Cod		17300-22900ng/L		2
	USA-La Pine Oregon		E0.4-320µg/L	>90	5
	USA - Jefferson & Summit County, Colorado		1.6-850µg/L		6
	USA-Montana		10^5ng/L		3
	USA -Montana		>877µg/L	>60	4
	USA-Colorado	0.5µg/L	450-9300[a c]µg/L	100	7
	USA-New England		>50µg/L		9
	USA-Colorado		20-44µg/L		11
	USA-Golden Colorado	0.2µg/L	21-44µg/L		12
	USA-Woodville Florida	0.015µg/L	>10µg/L		14
	USA-Skaneateles Lake New York	6.72ng/L	<RL-18,400ng/L		15
	USA-Greenville N. Carolina		35.5[b]µg/L		10
1,7-dimethylxanthine	USA-Cape Cod		54900-65100ng/L		2
	USA-La Pine Oregon		E58µg/L		5
	USA-Montana		10^5ng/L		3
	USA -Montana		>1010µg/L	>60	4
	USA-Colorado		21-56[a]µg/L		7
	USA-Woodville Florida	0.021µg/L	>10µg/L		14
Food additives					
Indole	USA-La Pine Oregon		<0.5-220µg/L	>90	5
Menthol	USA-La Pine Oregon		<0.5-160µg/L	>90	5
	USA-Woodville Florida	0.5µg/L	>10µg/L		14
Methyl Salicylate	USA-Colorado		1.6µg/L		7
Triethyl citrate	USA-LaPine Oregon		E0.1-11µg/L	>90	5
Industrial Compounds					
Surfactant Metabolites					
4-Nonylphenol	USA-Cape Cod		10-16µg/L		2
	USA-La Pine Oregon		<5-130µg/L	>90	5
	USA - Jefferson & Summit County, Colorado		<2-650µg/L		6
	USA-Colorado		58-340µg/L	63-88	7
	USA-Cape Cod	0.03µg/L	25-33µg/L		8
	USA-Colorado		2.4-11µg/L		11
	USA-Golden Colorado	2µg/L	2.4-6.1µg/L		12
	USA-North Carolina		78-210µg/L	100	13

Table A.A1 (Continued)

Compound	Country / Sampling Location	RL	Concentration	Detection Frequency (%)	Reference
Surfactant Metabolites					
NP1EC	USA-Cape Cod	1µg/L	7.8-8.2µg/L		2
	USA-Colorado		23-84µg/L		11
	USA-Golden Colorado		39-91µg/L±63		12
NP2EC	USA-Cape Cod		1.6-2.3µg/L		2
NP1EO	USA	1µg/L	3.5-E1000µg/L		6
	USA-Colorado		<RL-5.6µg/L		11
	USA-Golden Colorado		<RL-3.4µg/L±1.6		12
∑NPEO	USA-Cape Cod		3.9-4.8µg/L		2
	USA-Colorado		83-170[a]µg/L	70-79	7
∑NPEC	USA-Colorado		50-320[a]µg/L	91-100	7
∑OPEO	USA-Colorado	0.5µg/L	<RL-160µg/L	18	7
4-n-octylphenol	USA-Colorado		0.57-3.0[a]µg/L	3-12	7
4-t-octylphenol	USA-Colorado		1.6-220[a]µg/L	20-62	7
4-propylphenol	USA-Colorado		2.6-4.0µg/L	38-39	7
4-t-pentylphenol	USA-Colorado	0.5µg/L	<RL-0.66µg/L	6	7
4-Ethylphenol	USA-Colorado		7.5-15µg/L	57-65	7
4-Methylphenol	USA-Colorado		4500[a c] µg/L	97-100	7
Surfactants					
DAS	USA-Cape Cod		1670-2040ng/L		2
DSBP	USA-Cape Cod		2.8-6.5ng/L		2
UV Stabilizer / Antioxidant					
2,6-DTBP	USA-Colorado		<RL		7
Metal chelating agent					
NTA	USA-Colorado		69-130[a]µg/L	81-83	7
	USA- Colorado	0.02µg/L	1.3-6.5µg/L		12
EDTA	USA-Cape Cod		3.8-44.5µg/L		2
	USA		3.8-100µg/L		6
	USA-Colorado		110-1700µg/L	100	7
	USA- Colorado		8.2-37µg/L		11
	USA-Golden Colorado	0.1µg/L	10-34µg/L		12
Industrial Compounds					
Flame Retardants					
TCEP	USA-LaPine Oregon		E0.1-1.9µg/L	>90	5
TPP	USA-LaPine Oregon		<0.5-0.9µg/L	>90	5

Table A.A1 (Continued)

Compound	Country / Sampling Location	RL	Concentration	Detection Frequency (%)	Reference
Industrial Compounds					
Plasticizers					
TBEP	USA-New England		20µg/L		9
Bisphenol A	USA	0.003µg/L	0.094-0.15µg/L	75	8
	USA-Skaneateles Lake New York	10.3ng/L	<RL-14900ng/L	68	15
	USA	0.2µg/L	13µg/L	43	6
Disinfectants					
Phenol	USA-Woodville Florida	0.5µg/L	>10µg/L		14
P-cresol	USA-La Pine Oregon		1,300µg/L		5
	USA-Woodville Florida	1.0µg/L	>10µg/L		14
Fumigant					
1,2-dichlorobenzene	USA-Colorado		<RL(0.5µg/L)		7
1,3-dichlorobenzene	USA-Colorado		<RL(0.5µg/L)		7
Deodorizer					
1,4-dichlorobenzene	USA-Colorado		2.1-59[a]µg/L	13-35	7
Perfluorinated Compounds					
PFBS	USA-Skaneateles Lake New York	0.4ng/L	Nd-14.0ng/L ± 6.11	82	15
PFHxS	USA-Skaneateles Lake New York	0.2ng/L	Nd-2.48ng/L ± 1.50	89	15
PFOS	USA-Skaneateles Lake New York	0.2ng/L	Nd-94.4ng/L± 7.94	100	15
PFOSA	USA-Skaneateles Lake New York	0.4ng/L	Nd-6.56ng/L± 0.20	43	15
PFHxA	USA-Skaneateles Lake New York	0.4ng/L	3.67-99.0ng/L± 5.25	100	15
PFHpA	USA-Skaneateles Lake New York	0.4ng/L	Nd-12.9ng/L ±3.36	96	15
PFOA	USA-Skaneateles Lake New York	0.2ng/L	5.70-38.8ng/L ± 14.6	100	15
PFNA	USA-Skaneateles Lake New York	0.2ng/L	0.83-4.95ng/L ± 1.91	100	15
PFUnDA	USA-Skaneateles Lake New York	0.2ng/L	Nd-0.92ng/L ±0.24	57	15
PFDoDA	USA-Skaneateles Lake New York	0.2ng/L	Nd-5.91	32	15

Table A.A1 (Continued)

Compound	Country / Sampling Locations	RL	Concentration	Detection Frequency (%)	Reference
Other Compounds					
Repellents					
Anthraquinone	USA-Colorado	NA	1.1µg/L		
Benzene Metabolite					
1,4-benzoquinone	USA-Colorado	NA	2.6-3.1[a]µg/L	14-15%	7

1 - Carrara et al., (2008) **2** - Swartz et al., (2006) **3** - Godfrey et al., (2007) **4** - Godfrey & Woessner, (2004) **5** - Hinkle et al., (2005) **6** - Conn et al., (2010) **7** - Conn et al., (2006) **8** - Rudel et al., (1998) **9** - Phillips et al., (2015) **10** - Del Rosario et al., (2014) **11** - Conn & Siegrist, (2009) **12** - Conn et al., (2010) **13** - Stanford & Weinberg, (2010) **14** - Katz et al., (2010) **15** - Subedi et al., (2014); **DAS** (2-disulfonate); **DSBP** (4,4-bis(2sulfostryl)biphenyl); **DTBP** (2,6 di-t-butylphenol); **∑NPEO** (NP1EO - NP3EO); **∑NPEC** (NP1EC - NP3EC); **DEET** (N,N-diethyl-meta-toluamide); **PFBS** (Perfluoro butane sulfonate; **PFOS** (Perfluoro octane sulfonate); **PFOSA** (Perfluoro octane sulfonate); **PFHxA** (Perfluoro hexanoic acid); **PFHPA** (Perfluoro heptanoic acid; **PFOA** (Perfluoro octanoic acid); **PFNA** (Perfluoro nonanoic acid); **PFDA** (Perfluoro decanoic acid; **PFUnDA** (Perfluoro undecanoic acid); **PFDoDA** (Perfluoro dodecanoic acid); **NTA** (Nitro acetic acid); **EDTA** (Ethylenediamine acetic acid); **∑NPEC** (Sum of 4-nonylphenol mono-ethoxy carboxylate through 4-nonylphenol tetra-ethoxy carboxylate); **∑NPEO** (Sum of 4-nonylphenol mono-ethoxylate through 4-nonylphenol tetra-ethoxylate); **∑OPEO** (Sum of 4-tert-octylphenolmonoethoxylate through 4-tert-octylphenoltetraethoxylate); **TBEP** (tris (2-butoxyethyl) phosphate; **TPP** (Triphenyl phosphate); **TCEP** (tris(2-chloroethyl) phosphate; **NP1EC** (4-Nonylphenolmonoethoxycarboxylate); **NP2EC** (4-Nonylphenoldiethoxycarboxylate); **NPEO** (Nonylphenol Ethoxylates); **NPEC** (Nonylphenol Ethoxy carboxylate); Nd (not detected); **<RL** (less than reporting level); NA (Not available); μg^{-1} (microgram per liter); ng^{-1} (nanogram per liter)

Table A.A2 Summary Data for Concentrations, Sampling Locations and Detection Frequencies for EOCs in Downgradient Groundwater

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL)	References
Pharmaceuticals Analgesics & Anti-inflammatories							
Acetaminophen	USA	La Pine Oregon			<0.04-0.12µg/L		5
		Nebraska-shallow wells	19	26	0.015µg/L	0.0086µg/L	7
Diclofenac	Canada	Point Pelee-1 shallow well			<4-30ng/L		1
		Long Point-10m downgradient			1-30ng/L		1
		Lake Joseph			Nd		1
Ibuprofen	USA	Cape Cod			2400-6800ng/L		1
		La Pine Oregon			<0.04µg/L		5
		Nebraska-Shallow sand point well	19	5	0.129µg/L	0.018µg/L	7
		Greenville North Carolina	13	69	3.46µg/L		9
	Canada	Long Point Ontario			<7-12,000ng/L		1
		Lake Joseph Ontario			<8-2850ng/L		1
		Point Pelee Ontario			Nd		1
Ketoprofen	Canada	Long Point-20m downgradient			1-30ng/L		1
		Lake Joseph Ontario			Nd		1
		Point Pelee Ontario			Nd		1
Fenoprofen	Canada	Lake Joseph Ontario			Nd		1
		Point Pelee Ontario			Nd		1
		Long Point Ontario			Nd		1
Naproxen	Canada	Long Point site			<8-5580ng/L		1
		Lake Joseph Ontario			<8-160ng/L		1
		Point Pelee Ontario			Nd		1
Salicylic acid	Canada	Point Pelee-1 shallow well			<4-30ng/L		1
		Long Point-20m downgradient			<4-480ng/L		1
		Lake Joseph			4-6ng/L		1
Antipyrine	USA	Cape Cod-Massachusetts	20	5	1ng/L	1ng/L	6
		Cape Cod-Massachusetts		5	2ng/L	0.83ng/L	12
Indomethacin	Canada	Long Point-10m downgradient			1-30ng/L		1
		Lake Joseph Ontario			Nd		1
Codeine	USA	La Pine Oregon			<0.02µg/L		5
		Nebraska-Shallow sand point well	19	5	0.080µg/L	NA	7

Table A.A2 (Continued)

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL)	References
Analgesics & Anti-inflammatory							
Celecoxib	USA	New England			>0.1µg/L		8
Tramadol	USA	New England			>0.1µg/L		8
Antibiotics							
Erythromycin-H2O	USA	Nebraska-shallow sand point well	22	5	0.75µg/L	0.050µg/L	7
Sulfamethoxazole	USA	Cape Cod	20	60	113ng/L	0.1ng/L	6
		La Pine Oregon		NA	<0.06-0.10µg/L		5
		Nebraska-Shallow sand point well		8	0.15µg/L	0.23	7
		Frenchtown/Missoula City			10-450ng/L		3
		Montana			0.52-1.33µg/L		8
		New England	3	100	<RL-0.04µg/L	0.024µg/L	10
		Woodville-Florida		45	60ng/L	0.1ng/L	12
		Cape Cod - Massachusetts					
Sulfachloropyridazine		Cape Cod	20	10	0.7ng/L	0.58ng/L	12
Sulfamethizole	USA	Cape Cod	20	5	1ng/L	1ng/L	6
Sulfathiazole	USA	Cape Cod Massachusetts	20	5	0.2ng/L	0.27ng/L	12
Trimethoprim	USA	Cape Cod	20	5	0.7ng/L	0.1ng/L	6
		La Pine - Oregon		NA	<0.01µg/L		5
		Nebraska-Shallow sand point well	24	8	0.58µg/L	0.030µg/L	7
		Missoula City& Urban area		14	<25ng/L		3
		Montana			6.7[c]ng/L	0.5ng/L	11
		Liberty Bay & Puget Sound		5	1ng/L	0.1ng/L	12
		Washington					
		Cape Cod-Massachusetts					
Ciprofloxacin	USA	Nebraska-shallow sand point well	24	4	0.05TRµg/L	0.020µg/L	7
Enrofloxacin	USA	Nebraska-shallow sand point well	24	4	0.05TRµg/L	0.020µg/L	7
Sarafloxacin	USA	Nebraska-shallow sand point well	24	4	0.05TRµg/L	0.020µg/L	7
Beta Blockers							
Atenolol	USA	Cape Cod	20	5	0.8ng/L	0.1ng/L	6
Antihistamine							
Cimetidine	USA	La Pine Oregon			<0.1µg/L		5
Ranitidine	USA	La Pine Oregon			<0.1µg/L		5
Diphenhydramine	USA	La Pine Oregon			<0.01µg/L		5

Table A.A2 (Continued)

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL)	References
Lipid regulators							
Gemfibrozil	USA	Cape Cod Massachusetts	20	5	1.2ng/L	0.5ng/L	6
	USA	La Pine Oregon			<0.01µg/L		5
	USA	Cape Cod	20	5	0.3ng/L	0.15ng/L	12
	Canada	Long Point Ontario			<3-1950ng/L		1
		Lake Joseph Ontario			3-620ng/L		1
		Point Pelee Ontario			Nd		1
Bezafibrate	Canada	Long Point Ontario			<3-350ng/L		1
		Lake Joseph Ontario			Nd		1
Fenofibrate	Canada	Lake Joseph Ontario			Nd		1
		Point Pelee Ontario			Nd		1
		Long Point Ontario			Nd		1
Clofibric acid	Canada	Lake Joseph Ontario			<6-15ng/L		1
		Point Pelee Ontario			Nd		1
		Long Point Ontario			Nd		1
Simvastatin	USA	Cape Cod Massachusetts		5	14ng/L	3.0ng/L	12
Gemfibrozil	USA	Cape Cod Massachusetts	20	5	1.2ng/L	0.5ng/L	6
	USA	La Pine Oregon			<0.01µg/L		5
	USA	Cape Cod	20	5	0.3ng/L	0.15ng/L	12
	Canada	Long Point Ontario			<3-1950ng/L		1
		Lake Joseph Ontario			3-620ng/L		1
		Point Pelee Ontario			Nd		1
Antiepileptics							
Carbamazepine	USA	Cape Cod		25	72ng/L	0.5ng/L	6
	USA	La Pine-Oregon			<0.01µg/L		5
	USA	Frenchtown/Missoula City Montana			<25-210[b]ng/L		3
		Cape Cod-Massachusetts		25	62ng/L	0.068ng/L	12
Phenytoin	USA	Cape Cod-Massachusetts		20	66ng/L	2ng/L	6
		New England			>0.1µg/L		8
Primidone	USA	Cape Cod Massachusetts		10	9ng/L	2.1ng/L	12
Antiasthmatics							
Salbutamol	USA	La Pine Oregon			<0.2µg/L		5
Anti-coagulants							
Warfarin	USA	La Pine Oregon		5	<0.01µg/L	0.0061µg/L	5
		Nebraska-Shallow sand point well	19		0.009µg/L		7

Table A.A2 (Continued)

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL)	References
Steroids and hormones							
Estrone(E1)	USA	Cape Cod			BDL-120[a]ng/L		2
		New York			0.0042µg/L		8
17β-estradiol (E2)	USA	Cape Cod			BDL-45[a]ng/L		2
Estriol(E3)	USA	New York			0.0025µg/L		8
Estrone 3-sulphate (E1-3S)	USA	Cape Cod			1.0-4.0ng/L		2
Cis-testosterone	USA	Cape Cod	20	5	0.04ng/L	0.029ng/L	12
Progesterone	USA	Cape Cod	20	15	0.02ng/L	0.028ng/L	12
Cholesterol	USA	La Pine Oregon		5	BDL		5
		Colorado	18	22	3.5µg/L	0.5µg/L	4
Coprostanol		Colorado	18	25	10µg/L	0.5µg/L	4
Antihypertensives							
Diltiazem	USA	La Pine Oregon			<0.02µg/L		5
Dehydronifedipine (nifedipine	USA	La Pine Oregon			<0.02µg/L		5
metabolite)		Nebraska-Shallow sand point well	19	5	0.003µg/L	NA	7
Anthelmintic							
Thiabendazole	USA	La Pine Oregon			<0.01µg/L		5
Antidepressants							
Meprobamate	USA	Cape Cod Massachusetts	20	20	5.4ng/L	0.1ng/L	6
		Cape Cod-Massachusetts	20	15	2ng/L	0.1ng/L	12
		New England			>0.1µg/L		8
Butalbital	USA	New England			>0.1µg/L		8
Phenobarbital	USA	New England			>0.1µg/L		8
Carisoprodol	USA	New England			>0.1µg/L		8
Lidocaine (Anesthetics)	USA	New England			>0.1-0.5[b]µg/L		8
Antifungals							
Fluconazole	USA	New England			>0.1µg/L		8
Life style compounds							
Stimulants							
Caffeine	USA	Cape Cod		3	BDL-1710[a]ng/L		2
		La Pine Oregon		NA	<0.02-0.18µg/L		5
		Nebraska-shallow sand point well	19	47	0.120µg/L	0.014µg/L	7
		Missoula City & Urban area Montana	7	57	206ng/L		3
		Greenville North Carolina	6	33	0.99[c]µg/L	0.03mg/g	9
		Colorado	18	11	1.6µg/L	0.5µg/L	4
		Woodville-Florida			<1.0µg/L	0.5µg/L	10

Table A.A2 (Continued)

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL)	References
Stimulants							
1,7-dimethylxanthine	USA	Cape Cod			BDL-1730[a]ng/L		2
	USA	La Pine Oregon			<0.14µg/L		5
		Nebraska-shallow sand point well	19	32	0.022µg/L	0.019µg/L	7
		Woodville-Florida			<1.0µg/L	0.021µg/L	10
Personal Care Products							
Antimicrobial							
Triclosan	USA	Colorado	18		<RL	0.5µg/L	4
	Canada	Long Point Ontario			<4-6ng/L		1
		Lake Joseph Ontario			<4-7ng/L		1
		Point Pelee Ontario			Nd		1
Musk Fragrance							
Galaxolide	USA	New York			>0.1µg/L		8
		Woodville-Florida			<1.0µg/L		10
Tonalide	USA	La Pine Oregon		3-5[b]	BDL		5
Sunscreen							
Benzophenone	USA	New York			>0.1µg/L		8
Food additives							
Artificial Sweetener							
Acesulfame	USA	Cape Cod	20	85	5300ng/L	0.42ng/L	12
Stabilizer							
Triethyl citrate	USA	New York			>0.1µg/L		8
Antioxidants							
2[3]-t-Butyl-4-methoxyphenol	USA	Colorado	18		<RL	0.5µg/L	4
Industrial Compounds							
Surfactants							
DAS	USA	Cape Cod			BDL-4180[a]ng/L		2
DSBP	USA	Cape Cod			0.5-27[a]ng/L		2
Surfactant metabolites							
4-nonylphenol	USA	Cape Cod		14	BDL[a]-84µg/L	250	2
		Cape Cod	20		20ng/L(Estimated)		6
		New York			>0.1µg/L	2µg/L	8
		Colorado	18	6	3.0µg/L		4

Table A.A2 (Continued)

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL)	References
Surfactant Metabolite							
NP1EC	USA	Cape Cod			BDL-35µg/L		2
		Cape Cod	28	4	<RL	0.26	14
NP2EC	USA	Cape Cod			4.4a-69µg/L		2
∑NPEO	USA	Cape Cod			0.02a-5.0µg/L		2
		Colorado	18		<RL	2.0µg/L	4
∑NPEC	USA	Colorado	18	6	2.4µg/L	2.0µg/L	4
4-n-Octylphenol	USA	Colorado	18		<RL	0.5µg/L	4
4-t-Octylphenol	USA	New York			>0.1µg/L		8
		Colorado	18		<RL	0.5µg/L	4
∑OPEO	USA	Colorado	18		<RL	0.5µg/L	4
OP4EO	USA	Cape Cod	28	4	32.9µg/L		14
4-Propylphenol	USA	Colorado	18		<RL	0.5µg/L	4
4-t-Butylphenol	USA	Colorado	18		<RL	0.5µg/L	4
4-Ethylphenol	USA	Colorado	18		<RL	0.5µg/L	4
4-Methylphenol	USA	Colorado	18		0.53µg/L	0.5µg/L	4
4-t-Pentylphenol	USA	Colorado	18		<RL	0.5µg/L	4
2,6-Di-t-butylphenol	USA	Colorado	18		<RL	0.5µg/L	4
Metal chelating agents							
NTA	USA	Colorado	18		<RL	0.5µg/L	4
EDTA	USA	Cape Cod			3.8-44.5[a]µg/L		2
		Colorado	18	22	19µg/L	0.5µg/L	4
Perfluoro surfactants							
PFOA	USA	Cape Cod -water supply well		10	22ng/L	10ng/L	6
PFOS	USA	Cape Cod		40	97ng/L	1ng/L	6
				55	7ng/L	0.24ng/L	12
PFBS	USA	Cape Cod	20	55	23ng/L	0.22ng/L	12
PFHpA		Cape Cod	20	30	1ng/L	0.25ng/L	12
PFHxS	USA	Cape Cod	20	55	41ng/L	0.33ng/L	12
Disinfectants							
Phenol	USA	Woodville-Florida			<1.0µg/L	0.5µg/L	10
P-Cresol	USA	Minnesota	31	3	2.9µg/L		13
Flame Retardants							
TCEP	USA	Cape Cod		15	20ng/L	20ng/L	6
	USA	La Pine Oregon		6-15	BDL	0.04µg/L	5
	USA	New York			>0.1µg/L		8
		Liberty Bay & Puget Sound Washington			12.7-13.3 ng/L	10ng/L	11

Table A.A2 (Continued)

Compound	Country	Sampling Location	No of Sample	Detection Frequency (%)	Concentration ng/L or µg/L	Reporting Limits (RL	References
Flame Retardants							
TCPP	USA	Cape Cod		20	40ng/L	10ng/L	6
TDCPP	USA	Cape Cod		5	10ng/L	10ng/L	6
	USA	La Pine Oregon		10	BDL	0.1µg/L	5
		Woodville-Florida			<1.0µg/L		10
TEP	USA	Cape Cod		25	20ng/L	10ng/L	6
		Cape Cod	20	5	38ng/L	10ng/l	12
TBP	USA	La Pine Oregon		3-10[b]	<1µg/L		5
		USA	20	5	11ng/L		12
2-EHDP	USA	Cape Cod	20	10	15ng/L	1.5ng/L	12
Plasticizer							
Bisphenol A	USA	Cape Cod	20	5	4ng/L	2.5ng/l	12
		Cape Cod	28	21	>RL-0.044µg/L	0.004µg/L	14
TPP	USA	Cape Cod	20	5	14ng/L	1.5ng/L	12
TBEP	USA	Cape Cod		5	50ng/L	50ng/L	6
	USA	New York/New England		8	>0.1-20[b]µg/L		8
Fumigant							
1,2-dichlorobenzene	USA	Colorado	18		<RL	0.5µg/L	4
1,3-dichlorobenzene	USA	Colorado	18		<RL	0.5µg/L	4
Deodorizer							
1,4-dichlorobenzene	USA	Colorado	18		<RL	0.5µg/L	4
Fragrances /Flavoring							
2,6-Di-t-butyl-1,4-benzoquinone	USA	Colorado	18		<RL	0.5µg/L	4

1 - Carrara et al., (2008) **2** - Swartz et al., (2006) **3** - Godfrey et al., (2007) **4** - Conn & Siegrist, (2009) **5** - Hinkle et al., (2005) **6** - Schaider et al., (2014) **7** - Verstraeten et al., (2005) **8** - Phillips et al., (2015) **9** - Del Rosario et al., (2014) **10** - Katz et al., (2010) **11** - Dougherty et al., (2010) **12** - Schaider et al., (2016) **13** - Erickson et al., (2014)**PFBS** (Perfluoro butane sulfonic acid); **2-EHDP** (Ethyl hexyldiphenyl phosphate); **PFHpA** (Perfluoro heptanoic acid); **TBEP** (tris(2-butoxyethyl)phosphate; **TCEP** (tris(2-chloroethyl)phosphate; **TDCPP** (tris(1,3-dichloro-2-propyl)phosphate; **TBP** (Tributyl Phosphate); **TPP** (Triphenyl phosphate**); DEET** (N,N-diethyl-meta-toluamide); **PFOA** (perfluorooctanoic acid); **DAS** (2-disulfonate); **DSBP** (4,4-bis(2sulfostryl)biphenyl); **MBAS** (Methylene blue active substance); **∑NPEO** (NP1EO - NP3EO); **∑NPEC** (NP1EC - NP3EC); **DEET** (N,N-diethyl-meta-toluamide); **PFBS** (Perfluoro butane sulfonate; **PFOS** (Perfluoro octane sulfonate); **PFOSA** (Perfluoro octane sulfonate); **PFHxA** (Perfluoro hexanoic acid); **PFHPA** (Perfluoro heptanoic acid; **PFOA** (Perfluoro octanoic acid); **PFNA** (Perfluoro nonanoic acid); **PFDA** (Perfluoro decanoic acid; **PFUnDA** (Perfluoro undecanoic acid); **PFDoDA** (Perfluoro dodecanoic acid); **NTA** (Nitro acetic acid); **EDTA** (Ethylenediamine acetic acid); **∑NPEC** (Sum of 4-nonylphenol mono-ethoxy carboxylate through 4-nonylphenol tetra-ethoxy carboxylate); **∑NPEO** (Sum of 4-nonylphenol mono-ethoxylate through 4-nonylphenol tetra-ethoxylate); **OP4EO** (Octylphenol tetraethoxylate); **∑OPEO** (Sum of 4-tert-octylphenolmonoethoxylate through 4-tert-octylphenoltetraethoxylate); **NP1EC** (4-Nonylphenolmonoethoxycarboxylate); **NP2EC** (4-Nonylphenoldiethoxycarboxylate); **NPEO** (Nonylphenol Ethoxylates); **NPEC** (Nonylphenol Ethoxy carboxylate); **TBEP** (tris (2-butoxyethyl) phosphate; **TPP** (Triphenyl phosphate); **TCEP** (tris(2-chloroethyl) phosphate; Nd (not detected); **<RL** (less than Reporting Limit); **BDL** (Below Detection Level); **ng^{-1}** (nanogram per liter); µg^{-1} (microgram per liter)

Appendix B

Table A.B1 Survey Questionnaire

	SURVEY QUESTIONNAIRE
	Part 1: Socio-demographic, economic and housing characteristics
1	**Gender**: Male_____ Female____
2	**Age of respondent (Years)**: 20-29__ 30-39__ 40-49___ 50-59____ 60 and above__
3	**What is your current marital status:** Single----- Married ------ Separated ------- Divorced-------Widowed-----Rather not say---------_
4	**Which city/town do you currently live in**?_____ **Which of the following best describes the area?** Urban------- Suburban-------- Rural---------
5	**Which of the following best describes the level of education you have completed?** Elementary or less-----Secondary---------Technical/vocational--------College---------- University (or equivalent)----------
6	**What is your personal monthly income range in naira?** <50000____ 50000-100000____ 100000-150000----- 150000-200000------250000-300000----- 300000-350000------- >350000---------
7	**What is your combined monthly income range in naira?** <50000____ 50000-100000____ 100000-150000----- 150000-200000------250000-300000----- 300000-350000------- >350000
8	**How would you rate the financial situation in your household?** Very bad---------- Bad--------- Neither Good nor Bad-------- Good--------- Very Good----------
9	**Which of the following best describes your current household?** Single----- Single with children----Married with children------Married without children-------Other---------
10	**Which of the following best describes your toilet type?** Flush toilet --------- Pour flush ---------- Pit ----------Other ----------
11	**Do you have a septic system (soak away pit) in your compound?** Yes---------- No----------
12	**Which of the following is your main source of water supply?** Tap ---------- Borehole ---------- Well ---------- Stream ---------- Other ----------
13	**Please indicate what your main source of water supply is used for** Drinking ---------- Cooking ---------- Bathing ---------- Washing ---------- Other ----------
14	**Do you treat water before use?** Yes -------- No ---------. If Yes, please specify what chemical is used for water treatment ----------
	Part 2: Usage and disposal pattern for pharmaceuticals and personal care products and Pharmaceuticals
15	**How many times is laundry done in your household?** Once/week --- 2-3times/week ------4-5times/week ------- 5times or more/week------- Other-------
16	**After washing, how is dirty laundry water disposed of?** Flush in toilet---------- Outside the house---------- Inside the gutter ----------Other ----------
17	**Which of the following laundry product is used most often?** Detergent powder (OMO, Ariel, Klin, Jumbo jet) ---------Bar soap (Canoe, B29, Sunlight) -------Both Detergent & Laundry soap ---------- Other (Please specify) ---------None ---------
18	**Which of the following detergent pack size is used weekly in your household?** 1Kg---------- 500g----------250g----------100g----------Other (Please specify) ----------

Table A.B2 (Continued)

	Part 2 (Continued)
19	**Which of the following dish washing product is used most often in your household?** Liquid soap (Morning fresh, Mama Lemon, Fairy) --------- Dish washing powder (Tempo, Sunlight) ------Scouring powder (Vim, Ajax, Majik) ------ Dish washing bar (Bar soap, white soda) -------- Other ----------
20	**What size of dish washing liquid is used in your household weekly?** 1000 ml --------- 750 ml ---------- 500 ml ---------- 250 ml ---------- 100 ml -------- Other ---------
21	**Which of the following disinfectant is used most often in your household?** Harpic ---------- Bleach (Hypo, JIK, Parazone) ---------- Izal ---------- Other -------- None --------
22	**What quantity of disinfectant is consumed in your household weekly?** 1000 ml --------- 750 ml ---------- 500 ml ---------- 250 ml ---------- 100 ml ---------- Other -------
23	**Which of the following product is most often used in your household for bathing?** Antibacterial soap (Dettol, Delta, Roberts, Safe Guard) ---------- Toilet Soap (Premier, Lux, Imperial Leather, Eva) ---------- Both antibacterial/Toilet soap ----------
24	**Which of the following antiseptic liquid is most often used in your household?** Dettol ---------- Savlon ---------- Roberts ---------- TCP ---------- Other --------- None
25	**What size of antiseptic liquid is used in your household weekly?** 1000 ml ---------- 750 ml ---------- 500 ml ---------- 250 ml ---------- 100 ml ---------- Other -----
26	**Which of the following insecticide is most often used in your household?** Insecticide spray (Raid, Morten, Baygon, Rambo) -------- Insecticide Liquid (Snipper, DD Force, Sunami, Current) ---------- Other (Please specify) ----------
27	**What size of insecticide is used in your household weekly?** 1000 ml --------- 750 ml ----------500 ml ---------- 250 ml ---------- 100 ml ---------- Other -------
28	**How is your health in general? Would you say it is** Very bad ---------- Bad -------- Neither Good nor Bad ------- Good -------- Very Good ----------
29	**Have you taken any medicine in the past 24 hours**? Yes ---------- No ---------- Do not remember ---------- Prefer not to say ----------
30	**During the past 4 weeks, how many different medicines did you use?** None ---------- One ------- Two ----- Three------ Four ------- Five ------ Other ----------
31	**How often do you obtain medications without prescription?** Never ---------- Rarely -------- Sometimes ---------- Often ---------- Always ----------
32	**How often do you use analgesics (Pain killers)?** Never---------- Once/3months ---------- Once/month ----------2-3times/month ---------- Once/week ----------2-3times/week ----------Daily ---------- Do not Remember ----------
33	**Which of the following analgesics (pain killer) do you use most often?** Paracetamol --------- Panadol ---------- Novalgin --------- Ibuprofen -------- Other ----------
34	**How often do you use antimalarial drugs?** Never---------- Once/3months ---------- Once/month ----------2-3times/month ---------- Once/week ----------2-3times/week ----------Daily ---------- Do not Remember ----------
35	**Which of the following antimalarial drug do you use most often?** Chloroquine phosphate -------- Quinine --------- Coartem / Lonart -------- Artesunate ----- Other -----

Table A.B1 (Continued)

	Part 2 (continued)
36	**How often do you use antibiotics?** Never---------- Once/3months ---------- Once/month ----------2-3times/month ---------- Once/week ----------2-3times/week ----------Daily ---------- Do not Remember ----------
37	**Which of the following antibiotic do you use most often?** Tetracycline ---------- Chloramphenicol----------Ciprofloxacin ------ Ampicillin ---------- Ampiclox ---------- Septrin ---------- Other (Please specify ----------
38	**How often do you use antifungals?** Never---------- Once/3months ---------- Once/month ----------2-3times/month ---------- Once/week ----------2-3times/week ----------Daily ---------- Do not Remember ----------
39	**Which of the following antifungal do you use most often?** Canesten -------- Lamisil -------- Miconazole --------- Penicillin --------- Other ----------
40	**How often do you use cough and cold medicines?** Never---------- Once/3months ---------- Once/month ----------2-3times/month ---------- Once/week ----------2-3times/week ----------Daily ---------- Do not Remember ----------
41	**Which of the following cough & cold medicine do you use most often?** Benylin ------- Actifed ----- Robitusin ----- Cofta ------- Beehive ------ Other ----------
42	**Please specify any other medicine which you use most often** 1) ---------- 2) ---------- 3) ---------- 4) ---------- Please specify how often you use any medicine: ----------
43	**How do you typically dispose of any expired or unused medicines in your household?** Throw into the bin -------- Flush in toilet/sink ---------- Return to pharmacy ---------- Other ------
44	**How do you typically dispose of unwanted personal care products?** Throw into the bin ------- Flush in toilet/sink ---------- Resell / Give away to others --------- Other
	Part 3: Attitude and behavior towards the environment
45	**How concerned are you about the environment in general?** Not concerned ------Slightly concerned---------- Neutral ---------- Very concerned ---------- Extremely concerned----------
46	**How concerned are you about water pollution?** Not concerned ------- Slightly concerned------ Neutral ----- Very concerned---------- Extremely concerned----------
47	**Please indicate the extent to which you engage in the following activities** 1. Decide for environmental reasons to reuse something instead of throwing it away Never --------- Rarely --------- Sometimes ------- Often ------- Always-------- 2. Recycle items instead of throwing them away Never -------- Rarely ------- Sometimes ------- Often -------- Always---------- 3. Buy household products that you think are better for the environment Never ------ Rarely ------- Sometimes -------Often -------- Always---------- 4. Try to reduce water consumption Never -------- Rarely ---------- Sometimes ---------- Often ------- Always------ 5. Read ingredient list on products before buying them Never ---------- Rarely ------- Sometimes ---------- Often ---- Always----------

Table A.B1 (Continued)

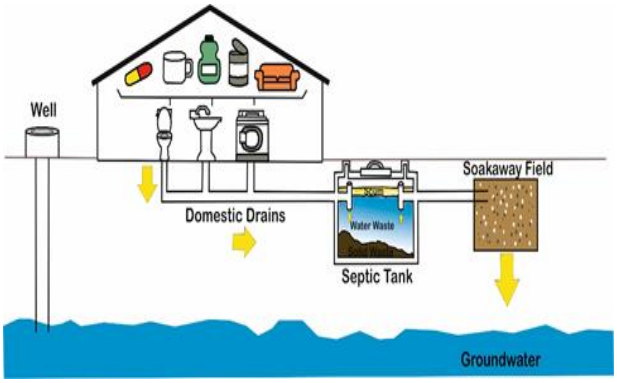
	Part 3 (Continued)
48	**Please indicate the degree to which you agree with the following statements** 1. Keeping the environment in a good state is important Strongly disagree----Disagree-------Neither agree/disagree-----Agree------Strongly agree------ 2. I would recycle more if there were convenient recycling facilities available Strongly disagree-------Disagree-------Neither agree/disagree-----Agree------Strongly agree--- 3. I would dispose of things properly if I knew were to take them Strongly disagree-------Disagree-------Neither agree/disagree-----Agree------Strongly agree--- 4. Government policies can adequately address environmental problems Strongly disagree-------Disagree-------Neither agree/disagree-----Agree-----Strongly agree------- 5. I have a personal responsibility to protect the environment Strongly disagree-------Disagree-------Neither agree/disagree-----Agree------Strongly agree------
	Part 4. Eliciting willingness to pay for groundwater protection program
	Daily, we use a variety of products, such as pharmaceuticals and personal care products to improve the quality of life. Pharmaceuticals are medicines we take to treat illness, disease and medical conditions. Personal care products include a variety of products we use daily, such as body soap, deodorants, shampoo, perfumes, hair dye, tooth paste, body lotion, cosmetics, amongst others. Other products include household chemicals used for general home care such as disinfectants, detergents, bleach, and insecticides. There is however, concern about the effects of these products on the environment and human health. This is because, these medicines can be excreted from the body and the personal care products can be rinsed from our bodies during bathing, and when we wash our clothes, dishes and clean our homes, different chemicals are released into the septic system (soak away pit), from where they can migrate to groundwater used for drinking and other domestic purposes. In addition, when we throw away unwanted medicines in trash, they can also find their way to groundwater from open dumps. Hence, properly functioning septic systems and the proper disposal of leftover medicines are necessary to protect groundwater resources. Below is the proposed intervention for groundwater protection 

Table A.B1 (Continued)

	Part 4 (Continued)
49	Let's assume you were presented with a groundwater protection program, which involves a medicine take-back program that will allow you return unwanted medicines to collection centers (like the pharmacy) and a government intervention scheme that will ensure that septic systems are properly maintained to minimize polluting groundwater, **1. Would you be willing to participate in a groundwater protection program?** Yes_____ No_____ **2. If you have answered yes, which would you prefer?** a) Medicine take back program only Yes_____ No_____ **b)** Government intervention scheme for wastewater management only Yes_____ No_____ **c)** Both medicine takeback program and Government intervention scheme Yes_____ No_____
50	Bearing in mind that contributing to a groundwater protection levy is an added taxation that would reduce your budget for other goods, please indicate from this list of possible sums, the range that best describes your maximum willingness to pay monthly fixed contribution to support the proposed groundwater protection program a) 500 – 2000 naira ☐ b) 2250-3750 naira ☐ c) 4000-5500 naira ☐
51	3) **If you have answered 'No', can you give the reason why you would not be willing to pay for groundwater protection program** a) The government should bear the cost ☐ b) I doubt the scheme would take place ☐ c) I pay enough taxes already ☐ d) I object to paying fees ☐ e) I do not use groundwater as a source of water supply ☐ f) I cannot afford to pay ☐

Table A.B2 Demographic, Socioeconomic and Housing Characteristics

Characteristics	Number (%)
Gender	
Male	169(48.3)
Female	181(51.7)
Age group (years)	
20-29	88 (25.1)
30-39	126 (36.0)
40-49	93 (26.6)
50-59	27 (7.7)
60+ years	16 (4.6)
Area of residence	
Urban	247 (70.6)
Rural	103 (29.4)
Highest level of education	
Elementary or less	11 (3.1)
Secondary	40 (11.4)
Technical	32 (9.1)
College	56 (16.0)
Undergraduate	118 (33.7)
Postgraduate	93 (26.6)
Monthly household income level (in Naira)	
<50,000	157 (44.9)
50,000-100,000	86 (24.6)
101,000-200,000	46 (13.1)
201,000-300,000	26 (7.4)
301,000-400,000	9 (2.6)
401,000-500,000	3 (0.9)
>500,000	23 (6.6)
Housing Type	
Apartment	146(41.7)
Private Residential	135(38.6)
Public Housing	58(16.6)
Rural Housing	11(3.1)
Toilet Type	
Flush Toilet	251(71.7)
Pour Flush	89(25.4)
Pit Latrine	11(3)

Table A.B3 Household monthly income as a predictor of WTP fee amount

Parameter Estimates									
Q61RR[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
N0.00	Intercept	3.266	.447	53.306	1	.000			
	Q9Household monthly income value	-.529	.108	23.986	1	.000	.589	.477	.728
N500-N2000	Intercept	3.359	.445	56.913	1	.000			
	Q9Household monthly income value	-.522	.106	24.129	1	.000	.593	.482	.731
N2250-N3750	Intercept	1.469	.494	8.822	1	.003			
	Q9Household monthly income value	-.269	.117	5.335	1	.021	.764	.608	.960

a. The reference category is: N4000 and above. There is statistically significant association between household monthly income and the amount participants are willing to pay for groundwater protection programs. As household income increases by one level, the odds of paying lower amounts as compared to higher amounts in the payment card decrease by 41% (p-value=0.0001, OR=.593) for the low fee category and by 24% (p-value = 0.021, OR=.764) for the medium fee category.

Table A.B4 Level of education as a predictor of WTP fee amount

Parameter Estimates									
Q61RR[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
N0.00	Intercept	5.658	1.432	15.620	1	.000			
	Level of education completed	-.777	.265	8.595	1	.003	.460	.273	.773
N500-N2000	Intercept	6.057	1.429	17.977	1	.000			
	Level of education completed	-.845	.265	10.193	1	.001	.430	.256	.722
N2250-N3750	Intercept	3.739	1.519	6.057	1	.014			
	Level of education completed	-.625	.284	4.833	1	.028	.535	.307	.934

a. The reference category is: N4000 and above.There is statistically significant association between the level of education completed and the amounts participants are willingness to pay for environmental protection measures. As education completed increased by one level, the odds of paying lower amounts as compared to higher amounts in the payment card decreased by 57% (p-value=0.001, OR=.430) for the lowest bid payment category and by 47% (p-value = 0.014, OR=.535) for the medium bid payment category.

Table A.B5 Age of participant as a predictor of WTP amount

Parameter Estimates									
Q61RR[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
N0.00	Intercept	1.458	.533	7.468	1	.006			
	Q2Age	.139	.216	.416	1	.519	1.149	.753	1.755
N500-N2000	Intercept	1.731	.528	10.725	1	.001			
	Q2Age	.067	.215	.097	1	.755	1.069	.702	1.630
N2250-N3750	Intercept	.641	.616	1.082	1	.298			
	Q2Age	-.040	.253	.025	1	.875	.961	.585	1.579

The reference category is: N4000 and above. Our results show that the impact of age on the fee participants are WTP is not statistically significant (p-value=0.755); but for every one-year increment in age, there will be a 6.9% (OR=1.069) increase in the probability that a participant will pay the lowest fee versus the highest fee in the payment card.

Table A.B6 Gender as a predictor of WTP amount

Parameter Estimates									
Q61RR[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
N0.00	Intercept	2.274	.397	32.807	1	.000			
	[Gender R=.00]	-.827	.485	2.911	1	.088	.438	.169	1.131
	[Gender R=1.00]	0[b]	.	.	0	.	.	.	.
N500-N2000	Intercept	2.497	.393	40.316	1	.000			
	[Gender R=.00]	-1.080	.482	5.019	1	.025	.340	.132	.874
	[Gender R=1.00]	0[b]	.	.	0	.	.	.	.
N2250-N3750	Intercept	1.099	.436	6.336	1	.012			
	[Gender R=.00]	-.927	.553	2.810	1	.094	.396	.134	1.170
	[Gender R=1.00]	0[b]	.	.	0	.	.	.	.

The reference category is: N4000 and above. We determined how gender can influence the choice for a payment category. Our results show that males compared to females were less likely to choose the low and medium payment categories than the high payment category. There is a statistically significant relationship between gender and the lowest bid category (p value=0.025). This means that it is 66% (OR=.340) more likely that females would be willing to pay the lowest bid amount (N500-N2000) as compared to the highest payment category.

APPENDIX C

Table A.C1 Retention time and mass spectrometry data, with precursor, quantifier (T1) and qualifier (T2) ions for target APIs

Compound	Retention Time (min)	Precursor (m/z)	Product T1, T2 (m/z)	Collision Energy T1, T2 (V)
Amitriptyline	12.45	278.2	191.1, 64.3	25.6, 17.4
Artemisinin	14.27	283.18	247.111, 209.111	10.253, 10.253
Atenolol	4.25	267.2	190, 145	19.2, 26.1
Caffeine	6.32	195.1	137.9, 110	20, 25
Carbamazepine	11.61	237.1	194.1, 192.1	25, 31
Cephalexin	17.08	348.272	174.058, 158.058	14.5, 10.253
Cetirizine	13.46	389.2	200.986, 166.111	18.545, 39.68
Cimetidine	4.31	253.15	159, 95.2	14.35, 24.2
Ciprofloxacin	6.74	332.15	314.111, 288.111	19.91, 17.787
Citalopram	9.99	325.2	262, 109.1	19.6, 26.5
Clarithromycin	13.71	748.6	590.44, 158.08	18.14, 26.1
Clotrimazole	15.15	345.139	277.04, 165.04	10.253, 32.146
Cloxacillin	12.53	436.03	220, 178	17.079, 24.713
Codeine	4.8	300.1	225.1, 215.1	26.5, 28.1
Cotinine	3.98	177.1	146.1, 98.1	15, 20
Desvenlafaxine	7.48	264.1	107.1, 58.3	30.3, 17.9
Diazepam	14.02	285	193, 154	31.7, 26.5
Diltiazem	11.1	415.1	177.9, 150	24.1, 42.1
Diphenhydramine	10.2	256	167.1, 152.1	10.3, 35.6
Enrofloxacin	6.95	360.16	316.17, 245.04	19.2, 26.58
Erythromycin	12.54	734.4	576.3, 158	15.2, 24.6
Fexofenadine	12.2	502.4	484.2, 466.2	20.3, 24.6
Fluconazole	7.88	307.1	238.1, 220.1	15, 15
Fluoxetine	12.77	310.178	148.111, 44.516	10.253, 10.253
Gabapentin	5.47	172.3	154, 137.1	11.8, 14.8
Hydrocodone	5.35	300.2	199, 171	29.5, 38.8
Itraconazole	16.24	705.32	432.294, 392.222	31.337, 35.433
Ketoconazole	13.57	531.1	489.1, 82.1	20, 45
Ketotifen	8.63	310.15	213, 96.222	28.91, 23.045
Lidocaine	6.66	235.15	86.2, 58.3	17.3, 32.75
Lincomycin	6.03	407.3	359.222, 126.222	18.798, 28.202
Loratadine	15.75	383.06	337.1, 267.1	23.2, 42.5
Metformin	1.39	130.2	71.3, 60.3	20.2, 11.7
Metronidazole	4.53	172.252	128.026, 82.312	10.253, 26.18
Miconazole	16.15	417.05	161, 159	30.073, 29.871
Naproxen	13.56	231.03	184.99, 170	13.39, 26.08
Nevirapine	9.07	267.1	226.2, 184.2	25, 35
Nicotine	1.92	163.18	130.111, 117.097	20.618, 26.888
Norethisterone	13.85	299.2	109.1, 83.2	26.5, 29.5

Table A.C1 (Continued)

Compound	Retention Time (min)	Precursor (m/z)	Product T1, T2 (m/z)	Collision Energy T1, T2 (V)
Norfluoxetine	12.9	296.15	134.111, 105.151	10.253, 15.511
Oseltamivir	10.67	313.2	225.05, 166.05	10.25, 18.4
Oxazepam	12.81	286.97	268.9, 240.9	10.25, 18.39
Oxytetracycline	7.08	461.16	426.11, 337	18.9, 29.52
Paracetamol	4.15	152	110.1, 93.1	14.2, 20.3
Pregabalin	5.47	160.059	124.169, 97.151	14.854, 14.061
Propranolol	9.88	260.2	183, 116.1	17.8, 18.2
Raloxifene	10.3	474.2	112.1, 84.3	30.9, 46.6
Ranitidine	4.33	315.2	176, 130	16.8, 24.6
Salbutamol	4.4	240.04	222.06, 148.06	10.35, 18.5
Sertraline	13.33	306.1	274.9, 159	19, 20
Sitagliptin	7.88	408.1	235, 174	18.25, 26.23
Sulfadiazine	4.3	248.98	185.04, 92.18	18.75, 37.96
Sulfamethoxazole	6.08	254.1	156, 108.1	17.7, 25.2
Temazepam	13.14	301.1	283, 255	13.1, 21.6
Tetracycline	6.93	445.15	410.111, 337	18.292, 28.657
Thiabendazole	8.15	202.1	175.1, 131.1	28, 35
Tramadol	7.51	264.1	58.4, 43.4	15.1, 50.3
Triamterene	7.07	254	237, 104	38, 60
Trimethoprim	6.16	291.15	261.1, 230.1	25, 24
Tylosin	12.43	916.57	772.52, 174.11	29.163, 38.011
Venlafaxine	9.41	278.16	260.14, 58.1	11.6, 20
Verapamil	11.18	455.3	165, 150	28.5, 38.4
		Internal Standards		
Amitriptyline D3	12.46	281.2	91.2	23.9
Atenolol D7	4.19	274.3	145.1	24.9
Atrazine D5	12.41	221.15	179.1	18.3
Carbamazepine D10	11.49	247.2	204	20.2
Ciprofloxacin D8	7.04	340.17	322.151	20.517
Citalopram D6	10.03	331.2	109.1	26.1
Codeine D6	4.71	306.27	218	23.25
Cotinine D3	3.98	180.1	80.1	25
Desvenlafaxine D6	7.22	270.2	64.3	17.4
Diazepam D5	13.95	290.1	198	33.8
Diltiazem D3	11.09	418.2	178	23.5
Diphenhydramine D3	10.2	259	167	11.2
Gabapentin D10	5.17	182.2	163.9	10.3
Hydrocodone D3	5.33	303.2	199.1	30.4
Itraconazole D4	16.24	709.35	454.333	31.135
Lidocaine D6	6.66	241.3	86.2	18.4
Metformin D6	1.39	136.2	77.3	21
Metronidazole D3	4.42	175.18	131.111	14.803

Table A.C1 (Continued)

Compound	Retention Time (min)	Precursor (m/z)	Product T1, T2 (m/z)	Collision Energy T1, T2 (V)
		Internal Standards		
Naproxen D3	13.8	234.15	188.111	12.933
Norfluoxetine D6	13.1	302.211	140.169	10.253
Oxazepam D5	12.7	292.15	274	10.25
Paracetamol D4	4.12	156.15	114.1	17.1
Propranolol D7	9.84	267.2	116.2	17.8
Raloxifene D4	10.15	478.2	116.2	29.4
Salbutamol D9	4.06	249.22	231.312	10.253
Sertraline D3	13.24	308.9	274.95	10.25
Sitagliptin D4	7.88	412.2	239.1	17.7
Sulfamethoxazole D4	6.73	258.2	160	16.7
Temazepam D5	13.09	305.8	260.1	22.4
Triamterene D5	7.03	259.2	242.1	27.9
Trimethoprim D9	5.95	300.2	234	24.2
Venlafaxine D6	9.45	284.2	121.1	28.1
Verapamil D7	11.16	462.4	165.1	29

Table A.C2: Summary data for total API detections in 53 groundwater samples from southern Nigeria

Well ID	AMT	ART	ATL	CAF	CMZ	CTZ	CMD	CIP	CTP	CMC	CMZ	COD	COT	DVX	DZP
LOD	2.96	3.37	2.78	15.1	0.74	3.13	1.77	11.9	1.32	14.4	19.8	0.73	7.43	3.4	1.47
LOQ	5.92	6.74	5.55	30.1	1.48	6.27	3.55	23.8	2.64	28.8	39.5	1.46	14.9	6.81	2.94
W_A	ND	ND	ND	86.7	ND	ND	46.8	12.3	ND	ND	ND	ND	ND	ND	ND
W_B	ND	ND	ND	234	1.96	ND	57.9	12	ND	ND	153	ND	11	ND	ND
W_C	ND	ND	ND	223	1.51	ND	ND	16.4	3.47	ND	127	ND	ND	ND	ND
W_E	ND	ND	ND	ND	1.17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_F	ND	ND	ND	ND	3.16	ND	ND	16	ND	ND	117	ND	ND	ND	ND
W_G	ND	ND	ND	573	ND	ND	2.98	28.3	ND	ND	109	ND	ND	ND	ND
W_J	ND	ND	ND	298	ND	ND	10.2	111	ND	ND	ND	ND	39.2	ND	ND
W_O	ND	ND	ND	228	112	ND	43.8	ND	ND	ND	ND	ND	8.01	ND	ND
W_W	8.61	ND	2.99	ND	ND	ND	79.8	31.4	ND	ND	132	ND	105	ND	ND
W_Z	ND	ND	3.33	38.3	ND	ND	16.7	47.7	ND	ND	ND	ND	17.7	5.23	ND
PH_11	3.4	ND	4.7	ND	ND	6.95	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_12	6.52	ND	ND	73.4	1.54	ND	ND	ND	1.34	ND	105	ND	24	ND	ND
PH_13	6.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_14	2.97	ND	ND	ND	ND	ND	ND	17.8	ND	ND	ND	ND	ND	ND	ND
PH_15	6.9	ND	8.91	297	2.23	6.94	ND	ND	ND	ND	ND	ND	26.5	ND	ND
PH_16	3.69	ND	ND	ND	ND	ND	ND	ND	1.54	ND	ND	ND	ND	ND	ND
PH_17	ND	ND	ND	ND	ND	4.13	4.71	ND	ND	ND	ND	ND	ND	ND	ND
PH_18	4.5	ND	ND	15.9	0.96	6.66	5.11	24.5	ND	ND	ND	ND	ND	ND	ND
PH_19	3.86	ND	ND	18.5	1.91	8.01	ND	ND	ND	ND	ND	ND	ND	ND	1.75
PH_20	ND	ND	ND	ND	10.8	ND	ND	25.9	ND	ND	ND	ND	ND	ND	1.89
PH_21	3.69	ND	ND	23.9	11.6	9.18	ND	ND	ND	72.1	ND	ND	ND	ND	ND
PH_22	ND	43.2	3.59	ND	ND	6.74	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_23	3.05	ND	ND	34.6	2.62	ND	212	ND	ND	ND	ND	ND	ND	4.23	ND
PH_24	3.4	ND	ND	ND	ND	5.32	2.75	ND	ND	ND	ND	ND	ND	ND	ND
PH_25	3.81	ND	ND	46.2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ENA	ND	ND	ND	123	355	7.17	ND	ND	ND	ND	ND	ND	38.9	ND	ND
ENB	ND	ND	3.26	241	122	8.75	395	ND	ND	90.8	ND	6.04	748	ND	4.29
ENC	3.2	ND	4.31	132	176	ND	441	ND	ND	118	ND	ND	108	ND	1.99
END	2.99	ND	ND	348	112	ND	ND	ND	ND	ND	ND	ND	79.8	ND	2.92
ENE	3.62	ND	2.79	ND	ND	ND	ND	ND	ND	ND	131	ND	ND	ND	ND
ENF	3.47	ND	ND	212	53.7	ND	8.38	15.1	ND	ND	ND	3.57	ND	ND	1.88
EN7	ND	ND	2.91	962	ND	ND	ND	ND	ND	ND	205	4.21	ND	ND	ND
EN8	ND	ND	5.22	148	34.2	ND	44.3	ND	ND	ND	180	ND	ND	ND	ND
EN9	ND	ND	ND	16.7	32.3	ND	ND	ND	ND	ND	ND	ND	7.9	7.9	ND
EN10	ND	ND	ND	20	140	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
EN11	ND	ND	ND	ND	4.74	ND	ND	ND	3.44	ND	177	ND	8.92	ND	ND
EN12	ND	ND	ND	367	126	ND	ND	ND	ND	ND	ND	ND	12.8	5.87	ND
EN13	ND	684	ND	ND	47.7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
EN14	ND	ND	ND	247	ND	ND	ND	ND	ND	ND	ND	ND	8.96	ND	ND
EN15	ND	381	ND	20.7	445	ND	2.23	ND	ND	ND	191	ND	ND	ND	ND
EN16	ND	ND	ND	82.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT26	ND	ND	ND	43.8	1.61	ND	ND	ND	ND	ND	146	ND	ND	ND	ND
PHT27	ND	ND	ND	ND	6.86	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT28	ND	ND	ND	65	1.07	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT29	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT30	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT31	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT32	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT33	ND	ND	ND	32.7	4.28	ND	495	ND	ND	ND	ND	ND	ND	ND	ND
PHT34	ND	ND	ND	ND	11	ND	2.98	ND	ND	ND	ND	ND	ND	ND	ND
PHT35	ND	ND	ND	306	14	ND	8.67	ND	ND	ND	ND	ND	ND	ND	ND
PHT36	ND	ND	ND	45.9	0.86	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT37	ND	ND	ND	185	0.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

AMT-amitriptyline; **ART**-artemisinin; **ATL**-atenolol; **CAF**-caffeine; **CMZ**-carbamazepine; **CTZ**-cetirizine; **CMD**-cimetidine; **CIP**-ciprofloxacin; **CTP**-citalopram; **CMC**-clarithromycin; **CMZ**-clotrimazole; **COD**-codeine; **COT**-cotinine**; DVX**-desvenlafaxine**; DZP**-diazepam; **LOD**-limit of detection; **LOQ**- limit of quantitation; ; >LOQ- ; <LOQ - ; ND – not detected.

Table A.C2 (continued)

Well ID	DTZ	DHM	EFX	ERT	FEX	FLZ	FXT	GPT	HDC	ITZ	KCZ	KTF	LDC	LMC	LTD
LOD	0.88	5.35	2.66	1.06	3.07	1.57	6.63	7.63	1.31	21.8	3.03	0.68	1.2	0.97	7.25
LOQ	1.76	10.7	5.32	2.13	6.14	3.13	13.3	15.3	2.63	43.7	6.06	1.37	2.41	1.94	14.5
W_A	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_B	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.12	ND
W_C	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_E	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_F	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_G	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	10.8	ND	ND
W_J	2.73	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_O	1.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
W_W	1.01	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	4.79	ND	ND
W_Z	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	3.45	146	ND
PH_11	ND	ND	ND	ND	ND	ND	ND	ND	2.47	ND	ND	1.2	ND	ND	ND
PH_12	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.72	ND	ND	ND
PH_13	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.82	ND	ND	ND
PH_14	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.22	ND	ND	ND
PH_15	1.58	ND	ND	ND	ND	ND	ND	ND	2.1	ND	ND	ND	ND	ND	ND
PH_16	ND	ND	ND	ND	ND	ND	ND	7.88	ND	ND	ND	ND	1.97	ND	ND
PH_17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_18	ND	ND	ND	ND	ND	ND	ND	ND	1.89	ND	ND	ND	ND	ND	ND
PH_19	ND	ND	ND	ND	ND	ND	ND	8.08	1.85	ND	ND	ND	ND	ND	ND
PH_20	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_21	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.93	ND
PH_22	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	3	ND	ND
PH_23	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_24	ND	ND	ND	ND	ND	ND	ND	ND	1.78	ND	ND	ND	ND	ND	ND
PH_25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ENA	ND	ND	ND	ND	ND	ND	ND	11.7	2.17	ND	ND	0.77	2.85	11.2	ND
ENB	ND	ND	ND	23.9	25	ND	ND	86.8	1.99	ND	ND	1.93	9.48	ND	ND
ENC	ND	ND	ND	ND	59.5	ND	ND	ND	2.59	ND	ND	ND	14.4	ND	ND
END	ND	ND	ND	ND	ND	ND	ND	ND	1.9	ND	ND	ND	5.46	28.6	ND
ENE	ND	ND	ND	ND	ND	ND	ND	27	ND	ND	ND	1.19	ND	ND	ND
ENF	ND	ND	ND	1.83	65.9	ND	ND	ND	ND	ND	ND	0.84	2.89	249	ND
EN7	ND	ND	ND	ND	ND	ND	67	ND	ND	ND	ND	ND	ND	ND	ND
EN8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	3.24	25.4	ND
EN9	ND	ND	ND	ND	ND	ND	ND	ND	3.83	ND	ND	ND	ND	4.16	ND
EN10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	5.8	13.7	ND
EN11	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	41.9	ND
EN12	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.58	ND	ND
EN13	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
EN14	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
EN15	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.97	2.25	ND
EN16	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	3.44	10.3	ND
PHT26	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.83	ND
PHT27	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT28	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	6.08	ND
PHT29	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT30	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT31	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT32	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT33	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT34	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT35	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.35	2.99	ND
PHT36	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT37	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

DTZ-diltiazem; **DHM**-diphenhydramine; **EFX**-enrofloxacin; **ERT**-erythromycin; **FEX**-fexofenadine; **FLZ**-fluconazole; **FXT**-fluoxetine; **GPT**-gabapentin; **HDC**-hydrocodone; **ITZ**- itraconazole; **KCZ**-ketoconazole; **KTF**-ketotifen; **LDC**-lidocaine; **LMC**-lincomycin; **LTD**-loratadine; > LOQ - ; <LOQ - ; ND – not detected

Table A.C2 (Continued)

Well ID	MFM	MTZ	MCZ	NPX	NVP	NCT	NTR	NFX	OSV	OXP	OXY	PCM	PGL	PNL	RXF
LOD	6.34	5.93	3.90	16.1	5.05	2.54	9.08	133.9	3.33	15.7	2.40	11.5	10.02	7.79	1.82
LOQ	12.7	11.9	7.80	32.2	10.10	5.08	18.2	267.9	6.66	31.4	4.80	23.1	20.05	15.59	3.65
W_A	13	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	437	ND	ND	ND
W_B	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	51.8	ND	ND	ND
W_C	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	24.5	ND	ND	ND
W_E	ND	ND	ND	21.1	ND	ND	ND	ND	3.59	ND	ND	225	ND	ND	ND
W_F	ND	ND	ND	24.5	ND	ND	ND	ND	ND	ND	ND	41.3	ND	ND	ND
W_G	ND	21.5	ND	162	ND	ND	ND	ND	ND	ND	ND	46.5	ND	ND	ND
W_J	ND	ND	ND	29.6	ND	ND	ND	ND	ND	ND	ND	48.9	ND	ND	ND
W_O	ND	ND	ND	32.4	ND	ND	ND	ND	ND	ND	ND	36.3	ND	ND	3.72
W_W	ND	ND	ND	30.8	ND	ND	ND	ND	ND	ND	ND	323	ND	ND	2.32
W_Z	ND	ND	ND	162	ND	ND	ND	ND	12.5	ND	ND	109	ND	ND	ND
PH_11	ND	ND	ND	234	ND	ND	13.5	ND	ND	ND	ND	ND	ND	ND	ND
PH_12	ND	ND	ND	ND	ND	ND	10.9	ND	ND	ND	ND	ND	ND	ND	ND
PH_13	ND	ND	ND	68	ND	ND	ND	ND	81.8	ND	ND	14	ND	ND	ND
PH_14	ND	ND	ND	22.7	ND	ND	16.3	ND	ND	ND	ND	ND	ND	ND	ND
PH_15	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	54.7	ND	ND	ND
PH_16	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	18.7	ND	ND	ND
PH_18	ND	ND	ND	16.6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_19	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	12.1	ND	ND	ND
PH_20	ND	ND	ND	100	ND	ND	27.1	ND	ND	ND	ND	16.2	ND	ND	ND
PH_21	108	ND	ND	23.1	ND	ND	ND	ND	ND	ND	ND	17.8	ND	ND	ND
PH_22	ND	ND	ND	113	ND	ND	32.8	ND	ND	ND	ND	ND	ND	ND	3.67
PH_23	ND	ND	ND	58.3	ND	ND	ND	ND	ND	ND	ND	14.5	ND	ND	ND
PH_24	ND	ND	ND	ND	ND	ND		ND	ND	ND	ND	55.3	ND	ND	ND
PH_25	ND	ND	ND	20.3	ND	ND	12.1	ND	ND	ND	ND	15.4	ND	ND	ND
ENA	14.1	14.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	18.3	ND	ND	ND
ENB	16.4	14.8	ND	ND	ND	ND	24.1	ND	ND	ND	ND	28.6	ND	ND	ND
ENC	378	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
END	59.2	ND	ND	23.7	ND	ND	ND	ND	161	ND	ND	ND	ND	ND	ND
ENE	ND	ND	ND	27.7	ND	ND	ND	ND	5.57	ND	ND	ND	ND	ND	ND
ENF	165	ND	ND	200	ND	ND	13	ND	ND	ND	ND	ND	ND	ND	ND
EN7	ND	ND	ND	18.8	ND	ND	ND	ND	ND	ND	ND	982	ND	ND	ND
EN8	19.5	ND	ND	28	ND	ND	ND	ND	ND	ND	ND	105	ND	ND	ND
EN9	ND	6.57	ND	27	ND	ND	ND	ND	ND	ND	ND	215	ND	ND	ND
EN10	ND	ND	ND	35	ND	ND	ND	ND	ND	ND	ND	14.9	ND	ND	ND
EN11	ND	ND	ND	16.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
EN12	ND	ND	ND	19	ND	ND	ND	ND	ND	ND	ND	124	ND	ND	ND
EN13	ND	ND	ND	ND	ND	ND	ND	482	ND	ND	ND	ND	ND	ND	ND
EN14	ND	ND	ND	36.2	ND	ND	ND	ND	ND	ND	ND	120	ND	ND	ND
EN15	ND	ND	ND	32.9	ND	ND	ND	ND	ND	ND	ND	20.4	ND	ND	ND
EN16	ND	ND	ND	17.1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT26	ND	ND	ND	37.7	ND	ND	ND	ND	3.51	ND	ND	ND	ND	ND	ND
PHT27	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT28	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT29	ND	ND	ND	17.6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT30	ND	ND	ND	25.3	ND	ND	ND	ND	3.53	ND	ND	15.8	ND	ND	ND
PHT31	ND	ND	ND	37.7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT32	ND	ND	ND	51.4	ND	ND	ND	ND	ND	ND	ND	11.7	ND	ND	ND
PHT33	ND	ND	ND	ND	ND	ND	ND	ND	3.48	ND	ND	96.4	ND	ND	ND
PHT34	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT35	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	49.3	ND	ND	ND
PHT36	ND	ND	ND	19.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT37	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

MFM-metformin; **MTZ**-metronidazole; **MCZ**-miconazole; **NPX**-naproxen; **NVP**-nevirapine; **NCT**-nicotine; **NTR**- norethisterone; **NFX**-norfluoxetine; **OSV**-oseltamivir; **OXP**-oxazepam; **OXY**-oxytetracycline; PCM-paracetamol; PGL-pregabalin; **PNL**-propranolol; **RXF**-raloxifene; >LOQ - ; <LOQ - ; ND – not detected

Table A.C2 (Continued)

Well ID	RTD	SBM	STL	SGT	SDZ	SMX	TZP	TET	TBZ	TMD	TTR	TMP	TYS	VFX	VPM
LOD	0.43	5.03	10.85	3.63	114.8	4.82	10.87	13.34	1.84	3.61	2.31	1.53	3.85	4.81	0.84
LOQ	0.85	10.1	21.70	7.26	229.6	9.65	21.74	26.67	3.68	7.22	4.63	3.06	7.70	9.61	1.68
W_A	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.09	ND	ND	2.47
W_B	ND	ND	ND	ND	ND	19.9	ND	ND	ND	ND	ND	3.91	ND	ND	ND
W_C	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	10.4	ND	ND	ND
W_E	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2
W_F	5.32	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.61
W_G	ND	ND	ND	ND	ND	73.9	ND	ND	ND	ND	ND	34.9	ND	ND	ND
W_J	ND	ND	ND	ND	ND	11.4	ND	ND	ND	ND	ND	10.9	ND	ND	ND
W_O	ND	ND	ND	ND	ND	4.97	ND	ND	ND	ND	ND	1.98	ND	ND	ND
W_W	ND	ND	ND	ND	ND	126	ND	ND	ND	ND	ND	11.8	ND	11.8	ND
W_Z	ND	ND	ND	ND	ND	19.8	ND	ND	ND	242	ND	37	ND	5.81	ND
PH_11	ND	ND	ND	ND	ND	5.41	ND	ND	ND	ND	ND	1.81	ND	ND	0.87
PH_12	ND	ND	ND	ND	ND	34.1	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_13	0.57	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.73	ND	ND	ND
PH_14	ND	ND	ND	ND	ND	31.3	ND	ND	ND	ND	ND	1.98	ND	ND	0.85
PH_15	ND	ND	ND	ND	ND	31.8	ND	ND	ND	ND	ND	1.9	ND	ND	ND
PH_16	4.09	ND	ND	ND	ND	5.38	ND	ND	ND	ND	ND	2.32	ND	5.13	ND
PH_17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.98	ND	ND	2.03
PH_18	ND	ND	ND	ND	ND	13.2	ND	ND	ND	ND	ND	5.7	ND	ND	0.93
PH_19	ND	ND	ND	ND	ND	148	ND	ND	ND	ND	ND	7.06	ND	ND	3.34
PH_20	ND	ND	ND	ND	ND	32.1	ND	ND	ND	ND	ND	ND	ND	ND	0.85
PH_21	0.79	ND	ND	ND	ND	169	ND	ND	ND	4.8	ND	5.49	ND	ND	ND
PH_22	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PH_23	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	19.7	ND	ND	ND
PH_24	0.45	ND	ND	ND	ND	184	ND	ND	ND	6.26	ND	3.53	ND	ND	ND
PH_25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.84
ENA	ND	ND	ND	ND	ND	126	ND	ND	ND	4.77	ND	1.91	ND	ND	ND
ENB	ND	63	ND	ND	ND	84.4	ND	ND	ND	357	ND	15.7	ND	ND	ND
ENC	ND	ND	ND	ND	ND	49.3	ND	ND	ND	71	ND	10.2	ND	ND	ND
END	ND	ND	ND	ND	ND	247	ND	ND	ND	ND	ND	17.1	ND	ND	ND
ENE	ND	ND	ND	ND	ND	12.9	ND	ND	ND	ND	ND	2.61	ND	ND	ND
ENF	5.32	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.8	ND	ND	1.7
EN7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.69	ND	ND	ND
EN8	ND	ND	ND	ND	ND	1253	ND	ND	ND	55.3	ND	25.6	ND	ND	ND
EN9	ND	ND	ND	ND	ND	189	ND	ND	ND	ND	ND	3.48	ND	ND	ND
EN10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	4.17	ND	ND	ND
EN11	ND	ND	ND	ND	ND	201	ND	ND	ND	ND	ND	9.9	ND	ND	ND
EN12	4.56	ND	ND	ND	ND	47.8	ND	ND	ND	105	ND	193	ND	ND	ND
EN13	ND	ND	ND	ND	ND	343	ND	ND	ND	7.38	ND	3.55	ND	ND	ND
EN14	ND	ND	ND	ND	ND	8	ND	ND	ND	ND	ND	8.03	ND	ND	ND
EN15	ND	ND	ND	ND	ND	ND	ND	ND	ND	17	ND	7.8	ND	ND	ND
EN16	ND	ND	ND	ND	ND	ND	ND	ND	ND	491	ND	5.19	ND	ND	0.95
PHT26	4.09	ND	ND	ND	ND	70.6	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT27	ND	ND	ND	ND	ND	37.8	ND	ND	ND	ND	ND	1.55	ND	ND	ND
PHT28	ND	ND	ND	ND	ND	81.6	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT29	ND	ND	ND	ND	ND	5.91	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT30	ND	ND	ND	ND	ND	40.4	ND	ND	ND	ND	ND	9.32	ND	ND	ND
PHT31	ND	ND	ND	ND	ND	39.2	ND	ND	ND	ND	ND	2	ND	ND	1.54
PHT32	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.52	ND	ND	ND
PHT33	ND	ND	ND	ND	ND	5	ND	ND	ND	ND	ND	1.82	ND	ND	1.6
PHT34	ND	ND	ND	ND	ND	43.2	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT35	ND	ND	ND	ND	ND	75.3	ND	ND	ND	ND	ND	4.95	ND	ND	ND
PHT36	ND	ND	ND	ND	ND	10.7	ND	ND	ND	ND	ND	ND	ND	ND	ND
PHT37	ND	ND	ND	ND	ND	10.5	ND	ND	ND	ND	ND	ND	ND	ND	0.91

RTD-ranitidine; SBM-salbutamol; **STL**-sertraline; **SGT**-sitagliptin; **SDZ**- sulfadiazine; **SMX**-sulfamethoxazole; **TZP**-temazepam; **TET**-tetracycline; **TBZ**-thiabendazole; TMD-tramadol; TTR-triamterene; TMP-trimethoprim; TYS-tylosin; VFX-venlafaxine; **VPM**-verapamil; >LOQ - ; <LOQ - ; ND – not detected.

Table A.C3 Summary of sampling locations, well depth and well distance from septic system drain field

Sample ID	Location	Temperature (^{0}C)	pH	Well depth (meters)	Setback distance (meters)
W_A	Enugu Street Port Harcourt	33	8.7	30	7
W_ B	Egbelu Close Port Harcourt	31	8.8	30	12
W_ C	Divine Grace Close	30	9.5	24	15
W_D	Pemac Avenue Port Harcourt	30	9.5	36	6
W_E	Egbelu Close Port Harcourt	29	9.4	30	10
W_ F	Mangrove Lane Port Harcourt	30	9.5	36	7
W_ G	Enugu Street Port Harcourt	32	7.5	24	12
W_J	Collins Onukem Close Port	30	7.8	30	7
W_W	Woji Road Port Harcourt	34	8.9	24	5
W_Z	Peace Close Port Harcourt	29	8.5	12	2
PH 11	Onukem Odara Street	29	8.6	30	11
PH 12	Woji Road	30	9.5	36	21
PH 13	Okporo Rd	30	9.4	30	5
PH 14	Power Encounter Ph	33	7.5	30	11
PH 15	Omaduma St	29	7.8	36	23
PH 16	Atuzie Crescent	33	9.5	30	12
PH 17	Eligbam Road	28	8.8	24	15
PH 18	Chinwo Street	27	7.5	36	12
PH 19	Onukem Odara Street	32	7.9	24	25
PH 20	Egbelu Close	29	8.0	30	16
PH 21	Birabi Street	29	8.5	30	24
PH 22	Chief Amadi Lane	28	9.2	36	22
PH 23	Eligbam Close	30	9.5	24	10
PH 24	Omerelu Street	29	8.0	30	15
PH 25	Orazi Road	33	8.5	30	8
PHT26	Elijiji Avenue	29	9.5	36	36
PHT27	Elijiji Crescent	30	8.0	24	22
PHT28	Ilom St Woji Road	31	8.7	30	14
PHT29	Gift Lane Woji	29	8.8	30	18
PHT30	Bonanza Road Elimgbu	33	8.5	24	10
PHT31	Road 13 Elimgbu	30	8.8	30	16
PHT32	Ogele Street Eliozu	28	8.0	36	18
PHT 33	Rumuevolu Rd Ada George	30	8.0	36	20
PHT34	Destiny Drive Mgbuogba	30	9.0	30	30
PHT35	Mission Ave Mgbuoba	32	8.7	24	25
PHT36	Ogunka St. Eneka	29	9.0	30	15
PHT37	Wokanma St. Eneka	33	7.5	30	25
PHT38	Farm Road Eneka	30	7.8	30	14
EN A	Amechi Street	29	5.5	11	20
EN B	Ugwuaji Street	33	7.5	7	15
EN C	Road 9 Trans Ekulu	28	8.1	8	18
EN D	Jona Agbo Street	29	7.8	12	9
EN E	Golf Estate GRA	30	6.5	11	10
EN F	Road 12 Trans Ekulu	31	6.8	10	15
EN7	Degema St. Ind. Layout	30	8.8	12	6
EN8	Ani Street Obiagu	33	8.5	10	15
EN9	Nnobi St. Ind. Layout	29	7.5	8	16
EN10	Udorji St Obiagu	29	7.5	10	28
EN11	Nawfia St. Ind. Layout	30	7.8	7	11
EN12	Nsugbe St. Ind. Layout	31	8.5	6	15
EN13	Umoji St. Ind. Layout	33	7.8	13	25
EN14	Ihiala St. Ind. Layout	30	6.8	11	31
EN15	Orifite Close Obiagu	29	5.5	10	28
EN16	Umunevo St. Obiagu	30	4.8	6	18

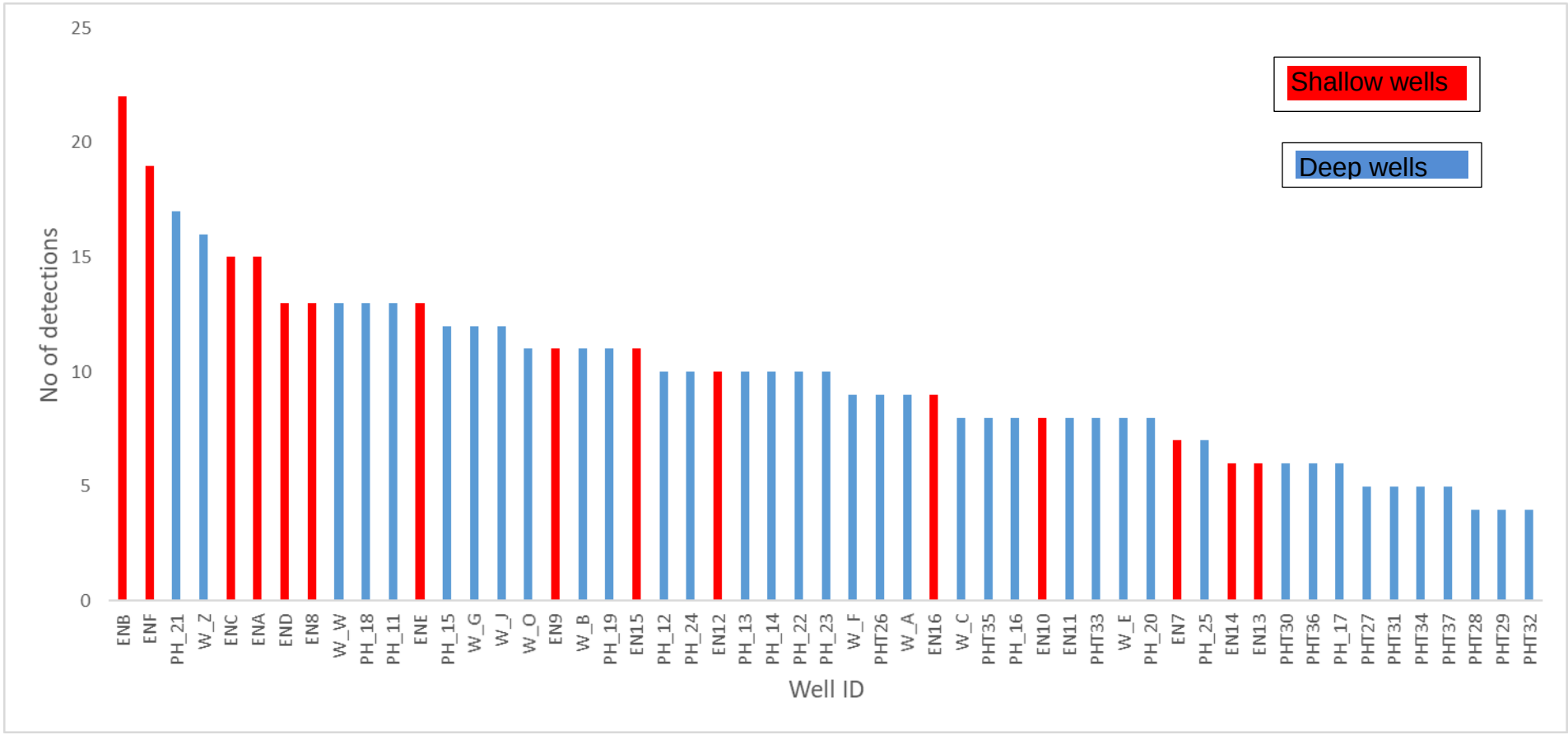


Figure A.C1 Number of API detections in domestic water wells

References

Access to Medicine Foundation. (2018). Access to Medicine Index 2018. AMF Report, pp. 1-257

Adekunle, I. M., Adetunji, M. T., Gbadebo, A. M., & Banjoko, O. B. (2007). Assessment of groundwater quality in a typical rural settlement in southwest Nigeria. International Journal of Environmental Research and Public Health, 4(4), 307–318.

Adelana, S. M. ., Olasehinde, P. ., Bale, R. B., Vrbka, P., Edet, A. E., & Goni, I. (2008). An overview of the geology and hydrogeology of Nigeria. In Applied groundwater studies in Africa Taylor & Francis, pp. 171–198.

Adelana, S. M. A., Abiye, T. A., Nkhuwa, D. C. W., Tindimugaya, C., & Oga, M. S. (2008). Urban groundwater management and protection in sub-saharan Africa. Applied Groundwater Studies in Africa, pp. 231–260.

Adesogan, S. (2013). Sewage Technology in Nigeria: A Pragmatic Approach. Science Journal of Environmental Engineering Research, 226(1991), 1–9.

Agunbiade, F. O., & Moodley, B. (2014). Pharmaceuticals as emerging organic contaminants in Umgeni River water system, KwaZulu-Natal, South Africa.Environ Monit Assess 186, 7273-7291

Ajibola, K. (2001). Design for comfort in Nigeria - a bioclimatic approach. Renewable Energy, 23(1), 57–76.

Al-Khazrajy, O. S. A., & Boxall, A. B. A. (2016). Risk-based prioritization of pharmaceuticals in the natural environment in Iraq. Environmental Science and Pollution Research, 23(15), 15712–15726.

Andreozzi, R., Marotta, R., Pinto, G., & Pollio, A. (2002). Carbamazepine in water: persistence in the environment, ozonation treatment and preliminary assessment on algal toxicity. Water Research 36, 2869 - 2877.

Anyusheva, M., Lamers, M., Schwadorf, K., & Streck, T. (2012). Analysis of pesticides in surface water in remote areas in Vietnam: Coping with matrix effects and test of long-term storage stability. International Journal of Environmental Analytical Chemistry, 92(7), 797–809.

Aronson, D., Boethling, R., Howard, P., & Stiteler, W. (2006). Estimating biodegradation half-lives for use in chemical screening. Chemosphere, 63(11), 1953–1960.

Ataguba, J. E., Ichoku, H. E., & Fonta, W. M. (2008). Estimating the willingness to pay for community healthcare insurance in rural Nigeria.PMMA Report, pp. 1-41

ATSDR. (1993). Dichlorvos: potential for human exposure.ATSDR Report, pp. 1-26

aus der Beek, T., Weber, F. A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., & Küster, A. (2016). Pharmaceuticals in the environment-Global occurrences and perspectives. Environmental Toxicology and Chemistry, 35(4), 823–835.

Auta, A., Banwat, S., Sariem, C., Shalkur, D., Nasara, B., & Atuluku, M. (2012). Medicines in Pharmacy Students' Residence and Self-medication Practices. Journal of Young Pharmacists, 4(2), 119–123.

Auta, A., Omale, S., Abanishe, S., & Abiodun, H. (2011). Unused medicines in Nigerian households: Types and disposal practices. Journal of Pharmacology and Pharmacotherapeutics, 2(3), 194 -196

Autino, B., Noris, A., Russo, R., & Castelli, F. (2012). Epidemiology of Malaria in Endemic Areas. Mediterr J Hematol Infect Dis Open Journal System Mediterr J Hematol Infect Dis, 4(10), 1-11.

Baker, D. R., & Kasprzyk-Hordern, B. (2013). Spatial and temporal occurrence of pharmaceuticals and illicit drugs in the aqueous environment and during wastewater treatment: new developments. The Science of the Total Environment, 454–455, 442–456.

Barber, L. B., Thurman, E. M., Schroeder, M. P., & Leblanc, D. R. (1988). Long-term fate of organic micropollutants in sewage-contaminated groundwater. Environmental Science & Technology, 22(2), 205–211.

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

Barnes, K. K., Kolpin, D. W., Furlong, E. T., Zaugg, S. D., Meyer, M. T., & Barber, L. B. (2008). A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States--I) groundwater. The Science of the Total Environment, 402(2–3), 192–200.

Beal, C. D., Gardner, E. a., & Menzies, N. W. (2005a). Process, performance, and pollution potential: A review of septic tank–soil absorption systems. Australian Journal of Soil Research, 43(7), 781.

Bengtsson-Palme, J., & Larsson, D. G. J. (2016). Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environment International, 86, 140–149.

Benner, J., Helbling, D. E., Kohler, H.-P. E., Wittebol, J., Kaiser, E., Prasse, C., … Boon, N. (2013). Is biological treatment a viable alternative for micropollutant removal in drinking water treatment processes? Water Research, 47(16), 5955–5976.

Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D., & Snyder, S. A. (2009). Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. Environmental Science and Technology, 43(3), 597–603.

Bercu, J. P., Morinello, E. J., Sehner, C., Shipp, B. K., & Weideman, P. A. (2016). Point of departure (PoD) selection for the derivation of acceptable daily exposures (ADEs) for active pharmaceutical ingredients (APIs).Regulatory Toxicology and Pharmacology, 79, 48 -56.

Bercu, J. P., Parke, N. J., Fiori, J. M., & Meyerhoff, R. D. (2008). Human health risk assessments for three neuropharmaceutical compounds in surface waters.Regulatory Toxicology and Pharmacology, 50, 420 - 427

Berto, J., Rochenbach, G. C., Barreiros, M. A. B., Corrêa, A. X. R., Peluso-Silva, S., & Radetski, C. M. (2009). Physico-chemical, microbiological and ecotoxicological evaluation of a septic tank/Fenton reaction combination for the treatment of hospital wastewaters. Ecotoxicology and Environmental Safety, 72(4), 1076–1081.

Besse, J.-P., & Garric, J. (2008). Human pharmaceuticals in surface waters Implementation of a prioritization methodology and application to the French situation. Toxicology Letters, 176, 104–123.

Beulke, S., & Brown, C. D. (2001). Evaluation of methods to derive pesticide degradation parameters for regulatory modelling. Biology and Fertility of Soils, 33(6), 558–564.

Biesterbos, J. W. H., Dudzina, T., Delmaar, C. J. E., Bakker, M. I., Russel, F. G. M., Von G??tz, N., Roeleveld, N. (2013). Usage patterns of personal care products: Important factors for exposure assessment. Food and Chemical Toxicology, 55, 8–17.

Bissell, P., Ward, P. R., & Noyce, P. R. (2001). The Dependent Consumer: Reflections on Accounts of the Risks of Non-Prescription Medicines. Health:, 5, 5–30.

Biswas, B., Qi, F., Biswas, J., Wijayawardena, A., Khan, M., & Naidu, R. (2018). The Fate of Chemical Pollutants with Soil Properties and Processes in the Climate Change Paradigm—A Review. Soil Systems, 2(3), 1-20.

Bloch, R., Monroy, J., & Fox, S. (2015). Urbanisation and Urban Expansion in Nigeria. Urbanization Report, pp. 1-73

Blondell, R. D., Azadfard, M., & Wisniewski, A. M. (2013). Pharmacologic therapy for acute pain. American Family Physician, 87(11), 766–772.

Boix, C., Ibáñez, M., Sancho, J. V, Rambla, J., Aranda, J. L., Ballester, S., & Hernández, F. (2014). Fast determination of 40 drugs in water using large volume direct injection liquid chromatography-tandem mass spectrometry. Talanta, 131, 719–727.

Bonansea, R., Amé, M., & Wunderlin, D. (2013). Determination of priority pesticides in water samples combining SPE and SPME coupled to GCâ€“MS. A case study: SuquÃ-a River basin (Argentina). Chemosphere, 90, 1860–1869.

Borchardt, M. a., Chyou, P. H., DeVries, E. O., & Belongia, E. a. (2003). Septic system density and infectious diarrhea in a defined population of children. Environmental Health Perspectives, 111(5), 742–748.

Bound, J. P., & Voulvoulis, N. (2005). Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environmental Health Perspectives, 113(12), 1705–1711.

Boxall, A. B. A. (2012). New and Emerging Water Pollutants arising from Agriculture. OECD Report, 1-48

Boxall, A. B. A., Fogg, L. A., Kay, P., Blackwell, P. A., Pemberton, E. J., & Croxford, A. (2003). Prioritisation of veterinary medicines in the UK environment. Toxicology Letters, 142(3), 207–218.

Boxall, A. B. a, Rudd, M. a, Brooks, B. W., Caldwell, D. J., Choi, K., Hickmann, S., Beazley, K. F. (2012). Review Pharmaceuticals and Personal Care Products in the Environment : What Are the Big Questions ?, 120(9), 1221–1229.

Boxall, A. B. a, Sinclair, C. J., Fenner, K., Kolpin, D., & Maund, S. J. (2004). When synthetic chemicals degrade in the environment. Environmental Science & Technology, 38(19), 368A-375A.

Bradley, B. R., Daigger, G. T., Rubin, R., & Tchobanoglous, G. (2002). Evaluation of onsite wastewater treatment technologies using sustainable development criteria. Clean Technologies and Environmental Policy, 4(2), 87–99.

Braund, R., Gn, G., & Matthews, R. (2009). Investigating unused medications in New Zealand. Pharmacy World and Science, 31(6), 664–669.

Bremer, J. E., & Harter, T. (2012). Domestic wells have high probability of pumping septic tank leachate. Hydrology and Earth System Sciences, 16(8), 2453–2467.

Bruce, G. M., Pleus, R. C., & Snyder, S. A. (2010). Toxicological relevance of pharmaceuticals in drinking water. Environmental Science and Technology, 44(14), 5619–5626.

Bucevska, V. (2000). Designing a web versus a paper questionnaire-some general and special issues. Public Opinion Quarterly Report, pp. 1–8.

Buck, R. C., Franklin, J., Berger, U., Conder, J. M., Cousins, I. T., Voogt, P. De, van Leeuwen, S. P. J. (2011). Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. Integrated Environmental Assessment and Management, 7(4), 513–541.

Bull, R. J., Crook, J., Whittaker, M., & Cotruvo, J. A. (2011). Therapeutic dose as the point of departure in assessing potential health hazards from drugs in drinking water and recycled municipal wastewater. Regulatory Toxicology and Pharmacology, 60(1), 1–19.

Burns, E. E., Carter, L. J., Kolpin, D. W., Thomas-Oates, J., & Boxall, A. B. A. (2018). Temporal and spatial variation in pharmaceutical concentrations in an urban river system. Water Research, 137, 72–85.

Burns, E. E., Carter, L. J., Snape, J., Thomas-Oates, J., & Boxall, A. B. A. (2018). Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. Journal of Toxicology and Environmental Health - Part B: Critical Reviews, 21(3), 115–141.

Cahill, J. ., Furlong, E. ., Burkhardt, M. ., Kolpin, D., & Anderson, L. . (2016). Determination of Pharmaceutical Compounds in Surface-and Ground-Water Samples by Solid-Phase Extraction and High-Performance Liquid Chromatography-Electrospray Ionization Mass Spectrometry Journal of Chromatography, 1041, 171–180.

Caliman, F. A., & Gavrilescu, M. (2009). Pharmaceuticals, personal care products and endocrine disrupting agents in the environment - A review. Clean, 37(4–5), 277–303.

Campbell, C. G., Borglin, S. E., Green, F. B., Grayson, A., Wozei, E., & Stringfellow, W. T. (2006). Biologically directed environmental monitoring, fate, and transport of estrogenic endocrine disrupting compounds in water: A review. Chemosphere, 65, 1265 -1289

Capleton, A. C., Courage, C., Rumsby, P., Holmes, P., Stutt, E., Boxall, B. A., & Levy, L. S. (2006). Prioritising veterinary medicines according to their potential indirect human exposure and toxicity profile. Toxicology Letters, 163, 213–223.

Carrara, C., Ptacek, C. J., Robertson, W. D., Blowes, D. W., Moncur, M. C., Sverko, E., & Backus, S. (2008). Fate of Pharmaceutical and Trace Organic Compounds in Three Septic System Plumes, Ontario, Canada. Environmental Science & Technology, 42(8), 2805–2811.

Carroll, S., Goonetilleke, A., & Dawes, L. (2004). Framework for soil suitability evaluation for sewage effluent renovation. Environmental Geology, 46, 195 - 208.

Carroll, S., Goonetilleke, A., Hargreaves, M., Carroll, S. P., Goonetilleke, A., & Hargreaves, M. (2004). Assessment of environmental and public health risk of onsite wastewater treatment systems. Proceedings of the tenth national symposium on individual and small community sewage systems, pp. 368–376.

Carroll, S., Goonetilleke, A., Thomas, E., Hargreaves, M., Frost, R., & Dawes, L. (2006). Integrated risk framework for onsite wastewater treatment systems. Environmental Management, 38(2), 286–303.

Carvalho, R. N., Ceriani, L., Ippolito, A., & Lettieri, T. (2015). Development of the first Watch List under the Environmental Quality Standards Directive . JRC Report, pp 1-168.

Charles, K. J., Ashbolt, N. J., Roser, D. J., Mcguinness, R., & Deere, D. A. (2005). Effluent quality from 200 on-site sewage systems: design values for guidelines. Water Science and Technology, 51, 163 - 169

Chiaia, A. C., Banta-Green, C., & Field, J. (2008). Eliminating solid phase extraction with large-volume injection LC/MS/MS: Analysis of illicit and legal drugs and human urine indicators in US wastewaters. Environmental Science and Technology, 42(23), 8841–8848.

Cho, S. H., Newman, D. H., & Bowker, J. M. (2005). Measuring rural homeowners' willingness to pay for land conservation easements, 7, 757–770.

Christensen, F. M. (1998). Pharmaceuticals in the Environment - A Human Risk? Regulatory Toxicology and Pharmacology. 28, 212–221.

Cliver, D. (2000). Research needs in decentralized wastewater treatment and management: Fate and transport of pathogens. In National Research Needs Conference Proceedings: Risk-based decision making for onsite wastewater treatment. USEPA Report, pp.122–151.

Coma, A., Modamio, P., Lastra, C. F., Bouvy, M. L., & Mariño, E. L. (2008). Returned medicines in community pharmacies of Barcelona, Spain. Pharmacy World and Science. 3, 272–277.

Conn, K. E., Barber, L. B., Brown, G. K., & Siegrist, R. L. (2006). Occurrence and fate of organic contaminants during onsite wastewater treatment. Environmental Science & Technology, 40(23), 7358–7366.

Conn, K. E., Siegrist, R. L., Barber, L. B., & Meyer, M. T. (2010). Fate of trace organic compounds during vadose zone soil treatment in an onsite wastewater system. Environmental Toxicology and Chemistry 29(2), 285–293.

Conn, K., Lowe, K., Drewes, J., Hoppe-Jones, C., & Tucholke, M. (2010). Occurrence of Pharmaceuticals and Consumer Product Chemicals in Raw Wastewater and Septic Tank Effluent from Single-Family Homes. Environmental Engineering Science, 27(4), 347–356.

Cooper, R. J. (2013). “I can’t be an addict. I am.” Over-the-counter medicine abuse: a qualitative study. BMJ, 3(6), 1-10.

Cunningham, V. L., Binks, S. P., & Olson, M. J. (2009). Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. Regulatory Toxicology and Pharmacology, 53(1), 39–45.

Cunningham, V. L., Perino, C., D’Aco, V. J., Hartmann, A., & Bechter, R. (2010). Human health risk assessment of carbamazepine in surface waters of North America and Europe. Regulatory Toxicology and Pharmacology, 56(3), 343–351.

Dankovic, D. A., Naumann, B. D., Maier, A., Dourson, M. L., & Levy, L. S. (2015). The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. Journal of Occupational and Environmental Hygiene, 12, 55–68.

Daughton, C. (2002). Environmental stewardship and drugs as pollutants. Journal of the Lancet, 360(10), 1035–1036.

Daughton, C.G. (2003). Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health. I. Rationale for and Avenues toward a Green Pharmacy. Environmental Health Perspectives, 111(5), 757–774.

Daughton, C. G. (2016). Pharmaceuticals and the Environment (PiE): Evolution and impact of the published literature revealed by bibliometric analysis. Science of The Total Environment, 562, 391–426.

Daughton, C. G., & Ruhoy, I. S. (2008). The afterlife of drugs and the role of pharmEcovigilance. Drug Safety, 31(12), 1069–1082.

Daughton, C. G., & Ruhoy, I. S. (2009). Environmental Footprint of Pharmaceuticals: the Significance of Factors Beyond Direct Excretion To Sewers. Environmental Toxicology and Chemistry, 28(12), 2495.

Daughton, C.G., & Ternes, T. a. (1999). Pharmaceuticals and personal care products in the environment: Agents of subtle change? Environmental Health Perspectives, 1079 6), 907–938.

Daughton, C.G. (2014). The Matthew Effect and widely prescribed pharmaceuticals lacking environmental monitoring: case study of an exposure-assessment vulnerability. The Science of the Total Environment, 466–467, 315–325.

Gaffney, J., Almeida, C. M. M., Rodrigues, A., Ferreira, E., Jo ~ Ao Benoliel, M.,Eepal, S. A. (2015). Occurrence of pharmaceuticals in a water supply system and related human health risk assessment. Water Research, 72, 199 -208

Del Rosario, K. L., Mitra, S., Humphrey, C. P., & O'Driscoll, M. a. (2014). Detection of pharmaceuticals and other personal care products in groundwater beneath and adjacent to onsite wastewater treatment systems in a coastal plain shallow aquifer. Science of the Total Environment, 487(1), 216–223.

Diamond, J. M., Latimer, H. A., Munkittrick, K. R., Thornton, K. W., Bartell, S. M., & Kidd, K. A. (2011). Prioritizing contaminants of emerging concern for ecological screening assessments. Environmental Toxicology and Chemistry 30(11), 2385–2394.

Dolan, D. G., Naumann, B. D., Sargent, E. V, Maier, A., & Dourson, M. (2005). Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regulatory Toxicology and Pharmacology 43, 1- 9

Dong, Z., Senn, D. B., Moran, R. E., & Shine, J. P. (2013). Prioritizing environmental risk of prescription pharmaceuticals. Regulatory Toxicology and Pharmacology, 65, 60 -67

Dougherty, J. a, Swarzenski, P. W., Dinicola, R. S., & Reinhard, M. (2010). Occurrence of herbicides and pharmaceutical and personal care products in surface water and groundwater around Liberty Bay, Puget Sound, Washington. Journal of Environmental Quality, 39(4), 1173–1180.

Dourson, M. L., Andersen, M. E., Erdreich, L. S., & Macgregor, J. A. (2001). Using Human Data to Protect the Public's Health. Regulatory Toxicology and Pharmacology, 33, 234–256.

Dourson, M. L., Felter, S. F., & Robinson, D. (1997). Evolution of science-based uncertainty factors in noncancer risk assessment. Human and Ecological Risk Assessment (HERA), 3(4), 579–589.

Drewes, J. E., Heberer, T., & Reddersen, K. (2002). Fate of pharmaceuticals during indirect potable reuse. Water Science and Technology, 46(3), 73–80.

Du, B., Price, A. E., Scott, W. C., Kristofco, L. a., Ramirez, A. J., Chambliss, C. K., Brooks, B. W. (2014). Comparison of contaminants of emerging concern removal, discharge, and water quality hazards among centralized and on-site wastewater treatment system effluents receiving common wastewater influent. Science of the Total Environment, 466–467, 976–984.

ECHA. (2012). Chapter R.8: Characterisation of dose [concentration]-response for human health: In Guidance on information requirements and chemical safety assessment. Helsinki, Finland.

Egeghy, P. P., Judson, R., Gangwal, S., Mosher, S., Smith, D., Vail, J., & Cohen Hubal, E. A. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159–166.

Ehirim, C. N., & Ofor, W. (2011). Assessing aquifer vulnerability to contaminants near solid waste landfill sites in a coastal environment, Port Harcout, Nigeria. Trends in Applied Sciences Research, 6(2), 165–173.

Ehirim, C., & Nwankwo, C. (2010). Evaluation of aquifer characteristics and groundwater quality. Archive of Applied Science Research, 2(2), 396–403.

Ekedahl, A. B. E. (2006). Reasons why medicines are returned to Swedish pharmacies unused. Pharmacy World and Science, 28(6), 352–358.

EMA. (2014). Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. EMA Report, pp. 2-11

EMEA. (1997). The European Agency for the Evaluation of medicinal products.EMA Report, 2-6

EMEA. (1998). Maximum Residue Limit. Enrofloxacin. Summary Report (2) EMEA/MRL/388/98-Final.

EPA, (n.d.). US EPA-Pesticides; Dichlorvos.EPA Report, pp.1-10

Erickson, Melinda, Langer, Susan, Roth, Jason and Kroening, S. (2014). Contaminants of Emerging Concern in Ambient Groundwater in Urbanized Areas of Minnesota.USGS Report, pp. 1-50

Escher, B., Eggen, R., Schreiber, Z., Wisner, B., & Schwarzenbach, R. (2002). Baseline Toxicity (Narcosis) of Organic Chemicals Determined by In Vitro Membrane Potential Measurements in Energy-Transducing Membranes. Environmen.Sci. Technol. 36, 1971 -1979

European Union (2012). Regulation (EU) No 649/2012 of the European Parliament and of the Council of 4 July 2012 concerning the export and import of hazardous chemicals.EU Report, 201/103

Bureau, E.C., (2003). Technical Guidance Documant on Risk Assessment Part II, Version, 2003. Guidance, pp.1-112

European Commission. (2013). DIRECTIVE 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC as regards priority substances in the firld of water policy. EU Report, 226, pp.1-15

European Commission (EC). (1980). Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption.

European Commission (EC). (2009). Assessment of the Antibiotic Resistance Effects of Biocides. EU Report, 1-87

Eze, C. L., & Eze, E. M. (2015). Investigation of Possible Groundwater Contamination from Septic System Siting in Port Harcourt , Nigeria. Journal of Natural Science Research, 5(10), 83–87.

Fàbrega, F., Marquès, M., Ginebreda, A., Kuzmanovic, M., Barceló, D., Schuhmacher, M., … Nadal, M. (2013). Integrated Risk Index of Chemical Aquatic Pollution (IRICAP): Case studies in Iberian rivers. Journal of Hazardous Materials, 263, 187–196.

Farouq, A. U., Suru, H. U., Uwerevu, E. O., & Ikpesu, J. E. (2018). Effects of Septic Tank on the Quality of Groundwater from Hand-Dug Wells in Effurun , Delta State , Nigeria, 3(1), 137–141.

Farouq AU, Suru HU, Uwerevu EO, & Ikpesu JE. (2018). Effects of Septic Tank on the Quality of Groundwater from Hand-Dug Wells in Effurun. International Research Journal of Advanced Engineering and Science, 3(1), 137–141.

Farré, M. la, Pérez, S., Kantiani, L., & Barceló, D. (2008). Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment. TrAC Trends in Analytical Chemistry, 27(11), 991–1007.

FDA. (2004). Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, manufacturing, and Quality Assurance. FDA Report, 1-19

Federal Ministry of Health. (2010). Access to and rational use of medicines at the household level. FMH Report, pp.1-33

Fent, K., Weston, A. A., & Caminada, D. (2006). Ecotoxicology of human pharmaceuticals. Aquatic Toxicology, 76(2), 122–159.

Fram, M. S., & Belitz, K. (2011). Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California. Science of The Total Environment, 409(18), 3409–3417.

Franco, A., Price, O. R., Marshall, S., Jolliet, O., Van den Brink, P. J., Rico, A., Ashauer, R. (2016). Toward refined environmental scenarios for ecological risk assessment of down-the-drain chemicals in freshwater environments. Integrated Environmental Assessment and Management, pp. 1-47

Fubara-Manuel, Isoteim, & Jumbo, R. B. (2014). The Effect of Septic Tank Locations on Borehole Water Quality in Port Harcourt, Nigeria. International Journal of Engineering and Technology, 4(5), 236–242.

Furlong, E. T., Kanagy, C. J., Kanagy, L. K., Coffey, L. J., & Burkhardt, M. R. (2014). Determination of Human-Use Pharmaceuticals in Filtered Water by Direct Aqueous Injection–High-Performance Liquid Chromatography/Tandem Mass Spectrometry. USGS Technical Report, pp. 1-60

Gandy, M. (2006). Water, Sanitation and the Modern City: Colonial and Post-colonial Experiences in Lagos and Mumbai, UNDP Report, pp. 1-30.

Gao, J., Linghua, A. E., Ae, L., Liu, X., Huaidong, A. E., Ae, Z., Wang, Z. (2009). The Occurrence and Spatial Distribution of Organophosphorous Pesticides in Chinese Surface Water. Bull. Environm. Contain. Toxicol, 82, 223–229.

Garcia, S. N., Clubbs, R. L., Stanley, J. K., Scheffe, B., Yelderman, J. C., & Brooks, B. W. (2013). Comparative analysis of effluent water quality from a municipal treatment plant and two on-site wastewater treatment systems. Chemosphere, 92(1), 38–44.

Gautier, C., Le Calvé, S., & Mirabel, P. (2003). Henry's law constants measurements of alachlor and dichlorvos between 283 and 298 K. Atmospheric Environment, 37(17), 2347–2353.

Giesy, J. P., & Kannan, K., (2002). Perfluorochemical surfactants in the environment. Environmental Science & Technology, 36(7), 146A-152A.

Glassmeyer, S. T., Hinchey, E. K., Boehme, S. E., Daughton, C. G., Ruhoy, I. S., Conerly, O., Thompson, V. G. (2009). Disposal practices for unwanted residential medications in the United States. Environment International, 35(3), 566–572.

Godfrey, E., & Woessner, W. W. (2004). Screening level study of pharmaceuticals in septic tank effluent and a wastewater treatment plant waste stream.Technical Report, pp. 1-13

Godfrey, E., Woessner, W. W., & Benotti, M. J. (2007). Pharmaceuticals in On-Site Sewage Effluent and Ground Water, Western Montana. Groundwater, 45(3), 263–271.

Gomes, R. L., Birkett, J. W., Scrimshaw, M. D., & Lester, J. N. (2005). Simultaneous determination of natural and synthetic steroid estrogens and their conjugates in aqueous matrices by liquid chromatography/mass spectrometry. International Journal of Environmental Analytical Chemistry, 85(1), 1–14.

Goossens, H., Ferech, M., Stichele, V., & Monique, E. (2005). Outpatient antibiotic use in Europe and assaciation with resistance: a cross-national database study. The Lancet, 365 (9459), 579–587.

Gottschall, N., Topp, E., Metcalfe, C., Edwards, M., Payne, M., Kleywegt, S., … Lapen, D. R. (2012). Pharmaceutical and personal care products in groundwater, subsurface drainage, soil, and wheat grain, following a high single application of municipal biosolids to a field. Chemosphere, 87(2), 194–203.

Grathwohl, P. (1990). Influence of Organic Matter from Soils and Sediments from Various Origins on the Sorption of Some Chlorinated Aliphatic Hydrocarbons: Implications on Koc Correlations. Environ. Sci. Technol, 24(2), 1687–1692.

Guillén, D., Ginebreda, A., Farré, M., Darbra, R. M., Petrovic, M., Gros, M., & Barceló, D. (2012). Prioritization of chemicals in the aquatic environment based on risk assessment: Analytical, modeling and regulatory perspective. Science of the Total Environment, 440, 236–252.

Guo, J., Sinclair, C. J., Selby, K., & Boxall, A. B. A. (2016). Toxicological and ecotoxicological risk-based prioritization of pharmaceuticals in the natural environment. Environmental Toxicology and Chemistry, 36, 1550 - 1159

Halling-Sørensen, B., Nors Nielsen, S., Lanzky, P. F., Ingerslev, F., Holten Lützhøft, H. C., & Jørgensen, S. E. (1998). Occurrence, fate and effects of pharmaceutical substances in the environment- A review. Chemosphere, 36(2), 357–393.

Hamunen, K., Laitinen-Parkkonen, P., Paakkari, P., Breivik, H., Gordh, T., Jensen, N. H., & Kalso, E. (2008). What do different databases tell about the use of opioids in seven European countries in 2002? European Journal of Pain, 12(6), 705–715.

Hayes, E. P., Jolly, R. A., Faria, E. C., Lovsin Barle, E., Bercu, J. P., Molnar, L. R., Weideman, P. A. (2016). A harmonization effort for acceptable daily exposure application to pharmaceutical manufacturing – Operational considerations. Regulatory Toxicology and Pharmacology, 79, 39–47.

Heberer, T. (2002). Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicology Letters, 131(1–2), 5–17.

Hilton, M. J., Thomas, K. V, & Ashton, D. (2003). Targeted monitoring programme for pharmaceuticals in the aquatic environment. R&D Technical Report P6 -012/06/TR, pp. 1-63

Hinkle, S. R., Weick, R. J., Johnson, J. M., Cahill, J. D., Smith, S. G., & Rich, B. J. (2005). Organic wastewater compounds, pharmaceuticals, and coliphage in ground water receiving discharge from onsite wastewater treatment systems near La Pine, Oregon: Occurrence and implications for transport. USGS Technical Report 2005-5055, pp. 1-108

Holmes, A. H., Moore, L. S. P., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., Piddock, L. J. V. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet, 387(10014), 176–187.

Houtman, C. J., Kroesbergen, J., Lekkerkerker-Teunissen, K., & van der Hoek, J. P. (2014). Human health risk assessment of the mixture of pharmaceuticals in Dutch drinking water and its sources based on frequent monitoring data. The Science of the Total Environment, 496, 54–62.

Howard, P. H., & Muir, D. C. G. (2011). Identifying New Persistent and Bioaccumulative Organics Among Chemicals in Commerce II: Pharmaceuticals. Environ. Sci. Technol, 45, 6938–6946.

Huber, M. M., Canonica, S., Park, G.-Y., & Gunten, U. V. (2003). Oxidation of Pharmaceuticals during Ozonation and Advanced Oxidation Processes.Environmental Science & Technology, 37, 1016 - 1024

Huggett, D. B., Cook, J. C., Ericson, J. F., & Williams, R. T. (2010). A Theoretical Model for Utilizing Mammalian Pharmacology and Safety Data to Prioritize Potential Impacts of Human Pharmaceuticals to Fish. Human and Ecological Risk Assessment, 9, 1789 -1799.

Hughes, S. R., Kay, P., & Brown, L. E. (2013). Global synthesis and critical evaluation of pharmaceutical data sets collected from river systems. Environmental Science and Technology, 47(2), 661–677.

Ibe, K. M., Nwankwor, G. I., & Onyekuru, S. O. (1999). Assessment of groundwater vulnerability and its application to the development of protection strategy for the water supply aquifer in Owerri, southeastern Nigeria. Environmental Monitoring and Assessment, 67, 323 -360

ICH Q3C. (2011). Impurities: guideline for residual solvents Q3C(R5) Step 4 version. In: International Conference on Harmonisation (ICH), Geneva. Geneva. ICH Report, 1-29

Inam, E., Offiong, N.-A., Kang, S., Yang, P., & Essien, J. (2015). Assessment of the Occurrence and Risks of Emerging Organic Pollutants (EOPs) in Ikpa River Basin Freshwater Ecosystem, Niger Delta-Nigeria. Bulletin of Environmental Contamination and Toxicology, 95(5), 624–631.

Jjemba, P. K. (2006). Excretion and ecotoxicity of pharmaceutical and personal care products in the environment. Ecotoxicology and Environmental Safety, 63(1), 113–130.

Jones, O. A. H., Voulvoulis, N., & Lester, J. N. (2004). Potential ecological and human health risks associated with the presence of pharmaceutically active compounds in the aquatic environment. Critical Reviews in Toxicology, 34(4), 335–350.

Jorgensen, B. S., & Syme, G. J. (2000). Protest responses and willingness to pay: Attitude toward paying for stormwater pollution abatement. Ecological Economics, 33(2), 251–265.

Jurado, A., Vàzquez-Suñé, E., Carrera, J., López de Alda, M., Pujades, E., & Barceló, D. (2012). Emerging organic contaminants in groundwater in Spain: A review of sources, recent occurrence and fate in a European context. Science of the Total Environment, 440, 82–94.

K'oreje, K. O., Vergeynst, L., Ombaka, D., De Wispelaere, P., Okoth, M., Van Langenhove, H., & Demeestere, K. (2016). Occurrence patterns of pharmaceutical residues in wastewater, surface water and groundwater of Nairobi and Kisumu city, Kenya. Chemosphere, 149, 238–244.

K'oreje, Kenneth Otieno, Kandie, F. J., Vergeynst, L., Abira, M. A., Van Langenhove, H., Okoth, M., & Demeestere, K. (2018). Occurrence, fate and removal of pharmaceuticals, personal care products and pesticides in wastewater stabilization ponds and receiving rivers in the Nzoia Basin, Kenya. Science of the Total Environment, 637–638(May), 336–348.

Kaiser, F. G., Wolfing, S., & Fuhrer, U. (1999). Environmental attitude and ecological behaviour. Journal of Environmental Psychology, 19, 1–19.

Kanu, K. C., Ijioma, S. N., & Atiata, O. (2016). Haematological, biochemical and antioxidant changes in wistar rats exposed to dichlorvos based insecticide formulation used in Southeast Nigeria. Toxics, 4(28), 1-10.

Katz, B. G., Griffin, D. W., & Davis, J. H. (2009). Groundwater quality impacts from the land application of treated municipal wastewater in a large karstic spring basin: Chemical and microbiological indicators. Science of the Total Environment, 407(8), 2872–2886.

Katz, B. G., Griffin, D. W., & McMahon, P. B. (2010). Fate of Effluent-Borne Contaminants beneath Septic Tank Drainfields Overlying a Karst Aquifer, 39(4), 1181–1195.

Katz, B. G., Griffin, D. W., McMahon, P. B., Harden, H. S., Wade, E., Hicks, R. W., & Chanton, J. P. (2010). Fate of effluent-borne contaminants beneath septic tank drainfields overlying a Karst aquifer. Journal of Environmental Quality, 39(4), 1181–1195.

Keegan, M., Kilroy, K., & Nolan, D. (2014). Assessment of the impact of traditional septic tank soakaway systems on water quality in Ireland, 70(4), 634–641.

Keller, V. (2006). Risk assessment of "down-the-drain" chemicals: Search for a suitable model. Science of the Total Environment, 360(1–3), 305–318.

Kephalopoulos, S., Bruinen de Bruin, Y., Arvanitis, A., Hakkinen, P., & Jantunen, M. (2007). Issues in consumer exposure modeling: towards harmonization on a global scale. Journal of Exposure Science & Environmental Epidemiology, 17, 90-100

Kimura, K., Hara, H., & Watanabe, Y. (2005). Removal of pharmaceutical compounds by submerged membrane bioreactors (MBRs). Desalination, 178(1–3), 135–140.

Kjellen, M., Pensulo, C., Nordqvist, P., & Fogde, M. (2011). Global Review of Sanitation System Trends and Interactions with Menstrual Management Practices.SEI Report, pp. 1-44

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, E. M., Zaugg, S. D., Barber, L. B., & Buxton, H. T. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. Environmental Science and Technology, 36(6), 1202–1211.

Kong, L., Kadokami, K., Duong, H. T., Thi, H., & Chau, C. (2016). Screening of 1300 organic micro-pollutants in groundwater from Beijing and Tianjin, North China. Chemosphere, 165, 221-230.

Kookana, R. S., Williams, M., Boxall, A. B. A., Larsson, D. G. J., Gaw, S., Choi, K., … Carriquiriborde, P. (2014). Potential ecological footprints of active pharmaceutical ingredients: an examination of risk factors in low-, middle- and high-income countries. Phil. Trans. R. Soc. B , 369 (1656), 20130586.

Kostich, M. S., Batt, A. L., Glassmeyer, S. T., & Lazorchak, J. M. (2010). Predicting variability of aquatic concentrations of human pharmaceuticals. Science of the Total Environment, 408(20), 4504–4510.

Kotchen, M., Kallaos, J., Wheeler, K., Wong, C., & Zahller, M. (2009). Pharmaceuticals in wastewater: Behavior, preferences, and willingness to pay for a disposal program. Journal of Environmental Management, 90(3), 1476–1482.

Kralik, M. (2015). How to Estimate Mean Residence Times of Groundwater. Procedia Earth and Planetary Science, 13, 301–306.

Krnic, D., Anic-Matic, A., Dosenovic, S., Draganic, P., Zezelic, S., & Puljak, L. (2015). National consumption of opioid and nonopioid analgesics in Croatia: 2007–2013. Therapeutics and Clinical Risk Management, 11, 1305–1314.

Kumar, A., Chang, B., & Xagoraraki, I. (2010). Human Health Risk Assessment of Pharmaceuticals in Water: Issues and Challenges Ahead. Int. J. Environ. Res. Public Health, 7, 3929–3953.

Kumar, A., & Xagoraraki, I. (2010). Human health risk assessment of pharmaceuticals in water: An uncertainty analysis for meprobamate, carbamazepine, and phenytoin. Regulatory Toxicology and Pharmacology, 57(2–3), 146–156.

Kümmerer, K. (2008). Pharmaceuticals in the environment : sources, fate, effects, and risks. Springer Science & Business Media.

Kümmerer, K. (2009). Antibiotics in the aquatic environment – A review – Part I. Chemosphere, 75, 417–434.

Kunkel, R., & Wendland, F. (1997). WEKU - A GIS-supported stochastic model of groundwater residence times in upper aquifers for the supraregional groundwater management. Environmental Geology, 30(1–2), 1–9.

Kusturica, M., Tomas, A., & Sabo, A. (2015). Diposal of unused drugs: Knowledge and behaviour among people around the world. Reviews of Environmental Contamination and Toxicology, Rev Environ. Contamin. Toxicol. 240, 1-104

Kuzmanović, M., Ginebreda, A., Petrović, M., & Barceló, D. (2015). Risk assessment based prioritization of 200 organic micropollutants in 4 Iberian rivers. Science of the Total Environment, 503–504, 289–299.

Lalone, C. A., Berninger, J. P., Villeneuve, D. L., & Ankley, G. T. (2014). Leveraging existing data for prioritization of the ecological risks of human and veterinary pharmaceuticals to aquatic organisms. Phil. Trans. R. Soc. B, 369(20140022).

Lamers, M., Anyusheva, M., La, N., Nguyen, V. V., & Streck, T. (2011). Pesticide Pollution in Surface-and Groundwater by Paddy Rice Cultivation: A Case Study from Northern Vietnam. Clean, 39(4), 356–361.

Lanigan, R. & Yamarik, T. A. (2002). Final Report on the Safety Assessment of BHT 1. International Journal of Toxicology, 21, 19–94.

Lapworth, D. J., Baran, N., Stuart, M. E., & Ward, R. S. (2012). Emerging organic contaminants in groundwater: A review of sources, fate and occurrence. Environmental Pollution 163, 287–303.

Leusch, F., Prochazka, E., Tan, B., Carswell, S., Neale P., Escher, B. (2012). Optimising micropollutants extraction for analysis of water samples : Comparison of different solid phase materials and liquid-liquid extraction. Urban Water Security Research Alliance, 191–195.

Lindström, A., Buerge, I. J., Poiger, T., Bergqvist, P. A., Müller, M. D., & Buser, H. R. (2002). Occurrence and environmental behavior of the bactericide triclosan and its methyl derivative in surface waters and in wastewater. Environmental Science and Technology, 36(11), 2322–2329.

Lorenzoni, I., Nicholson-Cole, S., & Whitmarsh, L. (2007). Barriers perceived to engaging with climate change among the UK public and their policy implications. Global Environmental Change, 17, 445–459.

Lowe, K., Rothe, N., Tomaras, J., DeJong, K., Tucholke, M., Drewes, J.,akata-Marr, J. (2007). Influent Constituent Characteristics of the Modern Waste Stream from Single Sources . WERF Report, pp. 1-256

Lowe, K. S., Tucholke, M. B., Tomaras, J. M. B., Conn, K., Hoppe, C., Drewes, J. E., Munakata-Marr, J. (2009). Influent Constituent Characteristics of the Modern Waste Stream from Single Sources. WERF Report, pp. 1-206.

Luo, Y., Guo, W., Ngo, H. H., Nghiem, L. D., Hai, F. I., Zhang, J., Wang, X. C. (2014). A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. The Science of the Total Environment, 473–474, 619–641.

Lusk, M., Toor, G. S., & Obreza, T. (2011a). Onsite Sewage Treatment and Disposal Systems : An Overview. UF Report, pp.1–8.

Lusk, M., Toor, G. S., & Obreza, T. (2011b). Onsite Sewage Treatment and Disposal Systems : Bacteria and Protozoa Sources and Types of Bacteria and Protozoa in Domestic Wastewater Behavior of Bacteria and Protozoa, UF Report, pp. 1–7.

Ma, J., Xiao, R., Li, J., Zhao, X., Shi, B., & Li, S. (2017). Determination of Organophosphorus Pesticides in Underground Water by SPE-GC – MS. Journal of Chromatographic Science, 47, 110–115.

Maal-Bared, R., Bartlett, K. H., Bowie, W. R., & Hall, E. R. (2013). Phenotypic antibiotic resistance of Escherichia coli and E. coli O157 isolated from water, sediment and biofilms in an agricultural watershed in British Columbia. Science of the Total Environment, 443, 315–323.

Mackay, D., & Webster, E. (2006). Environmental Persistence of Chemicals. ESPR-Environ Sci & Pollut Res, 13(1), 43–49.

Maloney, M. P., Ward, M. P., & Braucht, G. N. (1975). A revised scale for the measurement of ecological attitudes and knowledge. American Psychologist, 30(7), 787–790.

Manickum, T., & John, W. (2014). Occurrence, fate and environmental risk assessment of endocrine disrupting compounds at the wastewater treatment works in Pietermaritzburg (South Africa). Science of the Total Environment, 468–469, 584–597.

Manufacturing Pharma. (2015). PMG-MAN - Pharmaceutical Manufacturers Group of Manufacturers Association of Nigeria. http://www.manufacturingnigeria.com/pharma/show-info/market-overview/

Mao, Z., Zheng, X. F., Zhang, Y. Q., Tao, X. X., Li, Y., & Wang, W. (2012). Occurrence and biodegradation of nonylphenol in the environment. International Journal of Molecular Sciences, 13(1), 491–505.

Margot, J., Rossi, L., Barry, D. A., & Holliger, C. (2015). A review of the fate of micropollutants in wastewater treatment plants. Wires Water, 2(5), 457–487.

Martindale,W. and Sweetman, S. (2011). The Complete drug reference, London Pharmaceutical Press, pp.1-4688

Martinez-Hernandez, V., Meffe, R., Herrera Lopez, S., & de Bustamante, I. (2016). The role of sorption and biodegradation in the removal of acetaminophen, carbamazepine, caffeine, naproxen and sulfamethoxazole during soil contact: A kinetics study. Science of the Total Environment, 559, 232–241.

Massoud, M. A., Chami, G., Al-Hindi, M., & Alameddine, I. (2016). Assessment of Household Disposal of Pharmaceuticals in Lebanon: Management Options to Protect Water Quality and Public Health. Environmental Management, 57(5), 1125–1137.

Matamoros, V., García, J., & Bayona, J. M. (2008). Organic micropollutant removal in a full-scale surface flow constructed wetland fed with secondary effluent. Water Research, 42(3), 653–660.

Matamoros, V., Uggetti, E., García, J., & Bayona, J. M. (2016). Assessment of the mechanisms involved in the removal of emerging contaminants by microalgae from wastewater: a laboratory scale study. Journal of Hazardous Materials, 301, 197–205.

Mauclaire, A.-C., Lechat, P., Carton, A., Masset, D., Houeto, P., Guerbet, M., & Gatignol, C. (2011). Assessment of the health risks related to the presence of drug residues in water for human consumption: Application to carbamazepine. Regulatory Toxicology and Pharmacology, 62(1), 41–48.

Mbuligwe, S. E. (2004). Comparative effectiveness of engineered wetland systems in the treatment of anaerobically pre-treated domestic wastewater. Ecological Engineering, 23(4–5), 269–284.

McCall, P. J., Swann, R. L., Laskowski, D. A., Unger, S. M., Vrona, S. A., & Dishburger, H. J. (1980). Estimation of Chemical Mobility in Soil from Liquid Chromatographic Retention Times. Environm. Contam. Toxicol., 24, 190–195.

Medhi, B., Patyar, S., Rao, R. S., Ds, P. B., & Prakash, A. (2009). Pharmacokinetic and Toxicological Profile of Artemisinin Compounds: An Update. Pharmacology, 84, 323–332.

Meek, M. E., Renwick, A., Ohanian, E., Dourson, M., Lake, B., Naumann, B. D., & Vu, V. (2002). Guidelines for application of chemical-specific adjustment factors in dose/concentration-response assessment. Toxicology, 181-182; 115-120

Minnesota Department of Health. (2013). Health based guidance for water: Carbamazepine Toxicological Summary Sheet.MDH Report, pp.1-15

Minnesota Department of Health. (2015). Health based guidance for water: Toxicological Summary for acetaminophen.MDH Report, 1-15

Mompelat, S., Jaffrezic, A., Jardé, E., & Le Bot, B. (2013). Storage of natural water samples and preservation techniques for pharmaceutical quantification. Talanta, 109, 31-45

Monosson, E. (2005). Chemical Mixtures: Considering the Evolution of Toxicology and Chemical Assessment. Source: Environmental Health Perspectives, 113(4), 383–390.

Monteiro, S. ., & Boxall, A. B. A. (2010). Occurrence and fate of human pharmaceuticals in the environment. Reviews of Environmental Contamination and Toxicology.Springer, pp. 53-154

Morasch, B. (2013). Occurrence and dynamics of micropollutants in a karst aquifer. Environmental Pollution 173, 133–137.

National Population Commission. (2014). Nigeria- Demographic and Health Survey-2013 National Population Commission Federal Republic of Nigeria. ICF Report, pp. 1-565

Naumann, B. D., Weideman, P. A., Dixit, R., Grossman, S. J., Shen, C. F., & Sargent, E. V. (2008). Use of toxicokinetic and toxicodynamic data to reduce uncertainties when setting occupational exposure limits for pharmaceuticals. Risk Assessment: An International Journal, 3(4), 555–565.

Nielsen, J. L. (2016). Tooele County septic system density study.FINAL Report. pp.1-46

Nigeria Data Portal. (2016). Nigeria Census - Demographics. http://nigeria.opendataforafrica.org/

Nwankwoala, H. O., & Ngah, S. A. (2014). Groundwater resources of the Niger Delta: Quality implications and management considerations. International Journal of Water Resources and Environmental Engineering, 6(5), 155–163.

Obiadi, I. I., Obiadi, • C M, Akudinobi, • B E B, Maduewesi, • U V, & Ezim, • E O. (2016). Effects of coal mining on the water resources in the communities hosting the Iva Valley and Okpara Coal Mines in Enugu State, Southeast Nigeria. Sustainable Water Resources Management, 2, 207–216.

Odumodu, C. F. R., & Mode, A. W. (2017). Trace Fossils from the Campanian - Maastrichtian Enugu Formation of the Anambra Basin, South-eastern Nigeria: Implications for Paleoenvironmental Interpretation. Environmental Science, 2(8), 1–6.

Oluwasola, E., Okunade, O., & Adesina, K. (2017). Impact of the Proximity of Septic Tanks on the Bacteriological Quality of Well Water from Private House-holds in Ado Ekiti, Nigeria. Archives of Current Research International, 9(4), 1–8.

Oluyege, J. O., Dada, A. C., & Odeyemi, A. T. (2009). Incidence of multiple antibiotic resistant Gram-negative bacteria isolated from surface and underground water sources in south western region of Nigeria. Water Science and Technology, 59(10), 1929–1936.

Omonona, O. V, Onwuka, O. S., & Okogbue, C. O. (2014). Characterization of groundwater quality in three settlement areas of Enugu metropolis, southeastern Nigeria, using multivariate analysis. Environ. Monit Assess, 186, 651–664.

Onwuka, O. S., Omonona, • O V, & Anika, • O C. (2013). Hydrochemical characteristics and quality assessment of regolith aquifers in Enugu metropolis, southeastern Nigeria. Environ Earth Sci, 70, 1135–1141.

Onwuka, O. S., Uma, K. O., & Ezeigbo, H. I. (2004). Potability of shallow groundwater in Enugu town, southeastern Nigeria. Global Journal of Environmental Sciences, 3(1&2), 33–39.

Ortiz De García, S., Pinto, G. P., García-Encina, P. A., & Mata, I. (2013). Ranking of concern, based on environmental indexes, for pharmaceutical and personal care products: An application to the Spanish case. Journal of Environmental Management, 129, 384–397.

Paíga, P., Santos, L. H. M. L. M., & Delerue-Matos, C. (2017). Development of a multi-residue method for the determination of human and veterinary pharmaceuticals and some of their metabolites in aqueous environmental matrices by SPE-UHPLC–MS/MS. Journal of Pharmaceutical and Biomedical Analysis, 135, 75–86.

Parthasarathy, R., Monette, C. E., Bracero, S., & Saha, M. S. (2018). Methods for field measurement of antibiotic concentrations: Limitations and outlook. FEMS Microbiology Ecology, 94(8), 1–10.

Pavelic, P., Giordano, M., Keraita, B., Ramesh, V., & Rao, T. (2012). Groundwater availability and use in sub-Saharan Africa: A review of 15 countries. IWMI Report, pp. 1-289

Peček, G., Pavlović, D. M., & Babić, S. (2013). Development and validation of a SPE-GC-MS method for the determination of pesticides in surface water, International Journal of Environmental Analytical Chemistry, 93, 1311-1328

Pedersen, J. A., & Yeager, M. A. (2003). Xenobiotic Organic Compounds in Runoff from Fields Irrigated with Treated Wastewater. J. Agric. Food Chem. 2003, 51, 1360−1372.

Perazzolo, C., Morasch, B., Kohn, T., Smagnet, A., Thonney, D., & Chèvre, N. (2010). Occurrence and fate of micropollutants in the Vidy Bay of Lake Geneva, Switzerland. Part I: Priority list for environmental risk assessment of pharmaceuticals. Environmental Toxicology and Chemistry, 29(8), 1649–1657.

Petrović, M., Gonzalez, S., & Barceló, D. (2003). Analysis and removal of emerging contaminants in wastewater and drinking water. Trends in Analytical Chemistry, 22(10), 685–696.

Phillips, P., Schubert, C., Argue, D., Fisher, I., Furlong, E., Foreman, W., … Chalmers, A. (2015). Concentrations of hormones, pharmaceuticals and other micropollutants in groundwater affected by septic systems in New England and New York. Science of The Total Environment, 512–513, 43–54.

Piwoni, M. D., & Keeley, J. W. (1990). Basic concepts of contaminant sorption at hazardous waste sites. Ground Water Issue -EPA Report, pp. 1–25.

Pohl, K., Dulio, V., Schwarzbauer, J., & Rüdel, H. (2015). Environmental monitoring of biocides in Europe-compartment-specific strategies. NORMAN Report , pp. 1-45

Pomati, F., Orlandi, C., Clerici, M., Luciani, F., & Zuccato, E. (2008). Effects and interactions in an environmentally relevant mixture of pharmaceuticals. Toxicological Sciences, 102(1), 129–137.

Price, O. R., Hughes, G. O., Roche, N. L., & Mason, P. J. (2010). Improving emissions estimates of home and personal care products ingredients for use in EU risk assessments. Integrated Environmental Assessment and Management, 6(4), 677–684.

Qi, F., Kuppusamy, S., Naidu, R., Bolan, N. S., Ok, Y. S., Lamb, D.,Wang, H. (2017). Pyrogenic carbon and its role in contaminant immobilization in soils.Critical Reviews in Environmental Science and Technology. 47, 795-876

Quisumbing, A. (2003). Household Decisions, Gender, and Development: A Synthesis of Recent Research. IFPRI Report, pp.1-294

Rani, P. (2014). Factors influencing consumer behaviour. International Journal of Current Research and Academic Review, 54(6), 52–61.

Reichard, J. F., Maier, M. A., Naumann, B. D., Pecquet, A. M., Pfister, T., Sandhu, R., Johnson, J.. (2016). Toxicokinetic and toxicodynamic considerations when deriving health-based exposure limits for pharmaceuticals. Regulatory Toxicology and Pharmacology, 79, 67-78

Reilly, D., Singer, D., & Jefferson, A. (2015). Identification of local groundwater pollution in northeastern Pennsylvania : Marcellus flowback or not ? Environmental Earth Sciences, 73, 8097–8109.

Reuter, S., Gutterer, B., Sasse, L., & Panzerbieter, T. (2009). Decentralized Wastewater Treatment Systems (DEWATS) and Sanitation in Developimng Countries (Vol. 49). Loughbrough. WEDC Report, pp. 1-28

Richardson, B. J., Lam, P. K. S., & Martin, M. (2005). Emerging chemicals of concern: Pharmaceuticals and personal care products (PPCPs) in Asia, with particular reference to Southern China. Marine Pollution Bulletin, 50(9), 913–920.

Roberts, S., Higgins, C., & McCray, J. (2014). Sorption of emerging organic wastewater contaminants to four soils. Water (Switzerland), 6(4), 1028–1042.

Rotsidou, M., & Scrimshaw, M. D. (2015). An approach for prioritizing down-the-drain chemicals used in the household. International Journal of Environmental Research and Public Health, 12(2), 1351–1367.

Rowlands, I. H., Scott, D., & Parker, P. (2003). Consumers and green electricity: profiling potential purchasers. Business Strategy and the Environment, 12(1), 36–48.

Rudel, R. A., Melly, S. J., Geno, P. W., Sun, G., & Brody, J. G. (1998). Identification of Alkylphenols and Other Estrogenic Phenolic Compounds in Wastewater, Septage, and Groundwater on Cape Cod, Massachusetts. Environmental Science & Technology, 32(7), 861–869.

Rudel, R., Melly, S., Geno, P., Sun, G., & Brody, J. (1998). Identification of Alkylphenols and Other Estrogenic Phenolic Compounds in Wastewater, Septage, and Groundwater on Cape Cod, Massachusetts. Retrieved from http://lib3.dss.go.th/fulltext/Journal/Environ Sci. Technology 17,861-869.

Ruffino,B & Zanetti, M. (2009). Adsorption Study of Several Hydrophobic Organic Contaminants on an Aquifer Material Barbara Ruffino and Mariachiara Zanetti Department of Land , Environment and Geo-Engineering Politecnico di Torino, 5(4), 507–515.

Ruhoy, I. S., & Daughton, C. G. (2007). Types and quantities of leftover drugs entering the environment via disposal to sewage - Revealed by coroner records. Science of the Total Environment, 388(1–3), 137–148.

Ruhoy, I. S., & Daughton, C. G. (2008). Beyond the medicine cabinet: An analysis of where and why medications accumulate. Environment International, 34(8), 1157–1169.

Sallach, J. B., Snow, D., Hodges, L., Li, X., & Bartelt-Hunt, S. (2016). Development and comparison of four methods for the extraction of antibiotics from a vegetative matrix. Environmental Toxicology and Chemistry, 35(4), 889–897.

Santos, L. H. M. L. M., Araújo, A. N., Fachini, A., Pena, A., Delerue-Matos, C., & Montenegro, M. C. B. S. M. (2010). Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment. Journal of Hazardous Materials, 175, 45–95.

Sargent, E. V, Faria, E., Pfister, T., & Sussman, R. G. (2013). Guidance on the establishment of acceptable daily exposure limits (ADE) to support Risk-Based Manufacture of Pharmaceutical Products. Regulatory Toxicology and Pharmacology, 65, 242-250

Scandura, J. E., & Sobsey, M. D. (1997). Viral and bacterial contamination of groundwater from on-site sewage treatment systems. Water Science and Technology, 35(11–12), 141–146. h

Schaider, L. A., Rodgers, K. M., & Rudel, R. A. (2017). Review of Organic Wastewater Compound Concentrations and Removal in Onsite Wastewater Treatment Systems. Environmental Science and Technology, 51(13), 7304–7317.

Schaider, L., Ackerman, J., & Rudel, R. (2016). Septic systems as sources of organic wastewater compounds in domestic drinking water wells in a shallow sand and gravel aquifer. Science of The Total Environment, 547, 470–481.

Schaider, L., Ackerman Ruthann Rudel, J., Sarah Dunagan, M., & Julia Brody, M. (2011). Emerging Contaminants in Cape Cod Private Drinking Water Wells. SSI Report, pp.1-38

Schaider, L., Ph, D., Rodgers, K., & Rudel, R. (2013). Contaminants of Emerging Concern and Septic Systems : A Synthesis of Scientific Literature and Application to Groundwater Quality on Cape Cod, Report. SSI Report, pp.1-38.

Schaider, L., Rudel, R., Ackerman, J., Dunagan, S., & Brody, J. (2014). Pharmaceuticals, perfluorosurfactants, and other organic wastewater compounds in public drinking water wells in a shallow sand and gravel aquifer. Science of the Total Environment, 468–469, 384–393.

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.

Schulman, Lisa 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.

Schwab, B. W., Hayes, E. P., Fiori, J. M., Mastrocco, F. J., Roden, N. M., Cragin, D., … Anderson, P. D. (2005). Human pharmaceuticals in US surface waters: A human health risk assessment. Regulatory Toxicology and Pharmacology, 42(3), 296–312.

Sheppard, S., Long, J., & Sanipelli, B. (2009). Solid/liquid partition coefficients (Kd) for selected soils and sediments at Forsmark and Laxemar-Simpevarp. SGU Report, pp. 1-72

Siegrist, R. L., Lowe, K. S., Geza, M., & Mccray, J. E. (2012). Soil Treatment Units Used for Effluent Infiltration and Purification within Onsite Wastewater Systems: Science and Technology Highlights. International Symposium on Domestic Wastewater Treatment and Disposal Systems. CSM Report. pp.1-10

Siegrist, R., Tyler, E., & Jenssen, P. (2001). Design and performance of onsite wastewater soil absorption systems. IEPRI Report No. 1001446, pp.1-51

Sinclair, C. J., Boxall, A. B. A., Parsons, S. A., & Thomas, M. R. (2006). Prioritization of pesticide environmental transformation products in drinking water supplies. Environmental Science and Technology, 40(23), 7283–7289.

Slack, R. J., Gronow, J. R., & Voulvoulis, N. (2005). Household hazardous waste in municipal landfills: Contaminants in leachate. Science of the Total Environment, 337(1–3), 119–137.

Sorensen, J. P. R., Lapworth, D. J., Nkhuwa, D. C. W., Stuart, M. E., Gooddy, D. C., Bell, R. a., Pedley, S. (2014). Emerging contaminants in urban groundwater sources in Africa. Water Research, 72, 51–63.

Stackelberg, P. E., Furlong, E. T., Meyer, M. T., Zaugg, S. D., Henderson, A. K., & Reissman, D. B. (2004). Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant. The Science of the Total Environment, 329(1–3), 99–113.

Stackelberg, P. E., Gibs, J., Furlong, E. T., Meyer, M. T., Zaugg, S. D., & Lippincott, R. L. (2007). Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Science of the Total Environment, 377(2–3), 255–272.

Standley, L. J., Rudel, R. A., Swartz, C. H., Attfield, K. R., Christian, J., Erickson, M., & Brody, J. G. (2008). Wastewater-contaminated groundwater as a source of endogenous hormones and pharmaceuticals to surface water ecosystems. Environmental Toxicology and Chemistry, 27(12), 2457–2468.

Stanford, B. D., & Weinberg, H. S. (2010). Evaluation of on-site wastewater treatment technology to remove estrogens, nonylphenols, and estrogenic activity from wastewater. Environmental Science and Technology, 44(8), 2994–3001.

Stern, P., Dietz, T., & Guagnano, G. (1995). The new ecological paradigm in social-psychological context. Environment and Behaviour, 27(6), 723–743.

Stone, A., & Shiffman, S. (2002). Journaling about stressful events. Annals of Behavioral Medicine, 24(3), 190–200.

Straub, J. O., & Hutchinson, T. H. (2012). Environmental Risk Assessment for Human Pharmaceuticals: The Current State of International Regulations. Springer, pp. 17–47.

Stuart, M. E., Manamsa, K., Talbot, J. C., & Crane, E. J. (2011). Emerging contaminants in groundwater.BGS Report, pp.1-123

Subedi, B., Codru, N., Dziewulski, D. M., Wilson, L. R., Xue, J., Yun, S., Kannan, K. (2014). A pilot study on the assessment of trace organic contaminants including pharmaceuticals and personal care products from on-site wastewater treatment systems along Skaneateles Lake in New York State, USA. Water Research, 72, 28–39.

Sui, Q., Cao, X., Lu, S., Zhao, W., Qiu, Z., & Yu, G. (2015). Occurrence, sources and fate of pharmaceuticals and personal care products in the groundwater - A review. Emerging Contaminants, 2015, 1-11

Sussman, R. G., Naumann, B. D., Pfister, T., Sehner, C., Seaman, C., & Weideman, P. A. (2016). A harmonization effort for acceptable daily exposure derivation – Considerations for application of adjustment factors.Regulatory Toxicology and Pharmacology, 79, S57-66

Swartz, C. H., Reddy, S., Benotti, M. J., Yin, H., Barber, L. B., Brownawell, B. J., & Rudel, R. a. (2006). Steroid estrogens, nonylphenol ethoxylate metabolites, and other wastewater contaminants in groundwater affected by a residential septic system on cape cod, MA. Environmental Science and Technology, 40(16), 4894–4902.

Teerlink, J., Martínez-Hernández, V., Higgins, C. P., & Drewes, J. E. (2012). Removal of trace organic chemicals in onsite wastewater soil treatment units: A laboratory experiment. Water Research, 46(16), 5174–5184.

Temu, M. J., Kaale, E., & Marawiti, M. (2006). Storage of antimalarials at household level and associated factors in Kiromo ward, Bagamoyo Tanzania. African Health Sciences, 6(1), 43–48.

Teng, L., Xin, H. wen, Blix, H. S., & Tsutani, K. (2012). Review of the use of defined daily dose concept in drug utilisation reseacrh in China. Pharmacoepidemiology and Drug Safety, 21, 1118–1124.

Ternes, T. A., Kreckel, P., & Mueller, J. (1999). Behaviour and occurrence of estrogens in municipal sewage treatment plants - II. Aerobic batch experiments with activated sludge. Science of the Total Environment, 225(1–2), 91–99.

Ternes, T., Meisenheimer, M., Mcdowell, D., Sacher, F., Brauch, H. J., Haist-Gulde, B., Zulei-Seibert, N. (2002). Removal of Pharmaceuticals during Drinking Water Treatment. Environmental Science and Technology, 36, 3855 - 3863.

Ternes, T A, Joss, A., & Siegrist, H. (2004). Scrutinizing pharmaceuticals and personal care products in wastewater treatment. Environmental Science and Technology, 38(20), 392-399.

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

Teunissen-Ordelman, H., & Schrap, S. (1997). 1996 Aquatic Outlook. An analysis of issued pertaining to aquatic environments. Pesticides. RIZA Report, pp. 1-194.

Tomas, A., Paut Kusturica, M., Tomić, Z., Horvat, O., Djurović Koprivica, D., Bukumirić, D., & Sabo, A. (2017). Self-medication with antibiotics in Serbian households: a case for action? International Journal of Clinical Pharmacy. Springer, pp.1-7

Toor, G. S., Lusk, M., & Obreza, T. (2014). Onsite Sewage Treatment and Disposal Systems : Trace Organic Chemicals. UF Report, pp. 1-6

Trading Economics. (2019). Nigeria Urban Population.

Tuncel, S. G., Banu Öztas, N., Soner Erduran, M., & Banu, N. O. (2008). Air and Groundwater Pollution in an Agricultural Region of the Turkish Mediterranean Coast. Journal of the Air & Waste Management Association, 58(9), 1240–1249.

Turkish Medicines and Medical Devices Agency. (2017). Rational Drug Use-National Action Plan 2014-2017.TMA Report, pp.1-20

U.S. Environmental Protection Agency. (2009). Methodology for Risk-Based Prioritization Under ChAMP, USEPA Report., pp. 1-28

U.S Environmental Protection Agency. (1977). The report to Congress: Waste disposal practices and their effects on water.USEPA Report, pp. 1-101

UNDP. (2016). Annual Report Nigeria 2016. UNDP Report, pp.1-52

UNIDO. (2011). Pharmaceutical Sector Profile: Nigeria. UNIDO Report, 1-109

United Nations. (2011). Local Production of Pharmaceuticals and Related Technology Transfer in Developing Countries . UN Report, pp.1-326

US Environmental Protection Agency. (2016). EPI Suite^{TM}-Estimation Program Interface.

US EPA. (1997). Special report on Environmental endocrine disruption: An effects analysis. Genes & Development Vol. 11. USEPA Report, pp.1-120

US FDA. (2005). Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. USEPA Report, 1-30

USEPA. (2002a). A review of the reference dose and reference concentration processes. USEPA Report, pp.1-192

USEPA. (2002b). Onsite Wastewater Treatment Systems Manual. USEPA Manual, pp.2-369

USEPA. (2016). Method 542: Determination of Pharmaceuticals and Personal Care Products in Drinking Water by Solid Phase Extraction and Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry (LC/ESI-MS/MS). USEPA Report, pp. 1-39

van Gelder, M. M. H. J., Bretveld, R. W., & Roeleveld, N. (2010). Web-based Questionnaires : The Future in Epidemiology, 172(11), 1292–1298.

Vellinga, A., Cormican, S., Driscoll, J., Furey, M., O'Sullivan, M., & Cormican, M. (2014). Public practice regarding disposal of unused medicines in Ireland. Science of the Total Environment, 478, 98–102.

Versporten, A., Bolokhovets, G., Ghazaryan, L., Abilova, V., Pyshnik, G., Spasojevic, T., … Goossens, H. (2014a). Antibiotic use in eastern Europe: A cross-national database study in coordination with the WHO Regional Office for Europe. The Lancet Infectious Diseases, 14(5), 381–387.

Versporten, A., Bolokhovets, G., Ghazaryan, L., Abilova, V., Pyshnik, G., Spasojevic, T., … Goossens, H. (2014b). Antibiotic use in eastern Europe: A cross-national database study in coordination with the WHO Regional Office for Europe. The Lancet Infectious Diseases, 14(5), 381–387.

Verstraeten, I. M., Fetterman, G. S., Meyer, M. J., Bullen, T., & Sebree, S. K. (2005). Use of tracers and isotopes to evaluate vulnerability of water in domestic wells to septic waste. Ground Water Monitoring and Remediation, 25(2), 107–117.

Villa, S., Assi, L., Ippolito, A., Bonfanti, P., & Finizio, A. (2012). First evidences of the occurrence of polycyclic synthetic musk fragrances in surface water systems in Italy: Spatial and temporal trends in the Molgora River (Lombardia Region, Northern Italy). Science of the Total Environment, 416, 137–141.

Walters, E., Mcclellan, K., & Halden, R. U. (2010). Occurrence and loss over three years of 72 pharmaceuticals and personal care products from biosolidsesoil mixtures in outdoor mesocosms. Water Research, 44, 6011-6020

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

Wesley, S., & Zelezny, L. (1998). Values and Proenvironmental behaviour:A five-country survey. Journal of Cross-Cultural Psychologysychology, 29(4), 540–558.

Whitehead, J. H., & Geary, P. M. (2000). Geotechnical aspects of domestic on-site effluent management systems. Australian Journal of Earth Sciences, 47(1), 75–82.

WHO. (1998). Toxicological Evaluation of Certain Veterinary Drug Residues in Food. WHO Report, pp. 1-17.

WHO. (2003). Effective medicines regulation : ensuring safety, efficacy and quality. WHO Policy Perspectives on Medicines. WHO Report, pp. 1-6

WHOCC. (2015). Dermatologicals. WHO Report, pp.1-2

WHOCC. (2018). WHOCC - Definition and general considerations. WHO Report, pp.1-3

Wilkinson, C. F., Christoph, G. R., Julien, E., Michael Kelley, J., Kronenberg, J., McCarthy, J., & Reiss, R. (2000). Assessing the Risks of Exposures to Multiple Chemicals with a Common Mechanism of Toxicity: How to Cumulate? Regulatory Toxicology and Pharmacology 31, 30–43

Wilkinson, J. L., Boxall, A. B. A., & Kolpin, D. W. (2019). A novel method to characterise levels of pharmaceutical pollution in large-scale aquatic monitoring campaigns. Applied Sciences, 9(7), 1-14.

Wilson, M. P., & Schwarzman, M. R. (2009). Toward a new U.S. chemicals policy: Rebuilding the foundation to advance new science, green chemistry, and environmental health. Environmental Health Perspectives, 117(8), 1202–1209.

World Health Organization. (2004). The World Medicines Situation. WHO Report, pp.1-151.

World Health Organization. (2014). The evolving threat of antimicrobial resistance: Options for action. WHO Publications, pp.1–119.

World Health Organization. (2015a). 19th WHO Model List of Essential Medicines. WHO Report, pp.1-55.

World Health Organization. (2015b). Guidelines for the treatment of malaria.WHO Report, pp.1-317

Ying, G.-G., Williams, B., & Kookana, R. (2002). Environmental fate of alkylphenols and alkylphenol ethoxylates--a review. Environment International, 28(3), 215–226.

Yu, X., Mao, Y., Sun, J., & Shen, Y. (2014). Prioritizing chemicals for environmental management in China based on screening of potential risks. Front. Earth Science, 8(1), 104–114.

Zanto, T. P., Hennigan, K., Östberg, M., Clapp, W. C., & Gazzaley, A. (2011). Integrative Chemical-Biological Read-Across Approach for Chemical Hazard Classification, 46(4), 564–574.

Zhu, R., Zheng, H., & Liu, C. (2010). Estimation of groundwater residence time and recession rate in watershed of the Loess Plateau. Journal of Geographical Sciences, 20(2), 273–282.