UNIVERSITY OF CAPE COAST

DISTRIBUTION OF PHARMACEUTICALS AND ENDOCRINE DISRUPTORS IN RAW AND TAP WATER FROM CAPE COAST AND TAKORADI METROPOLISES

HENRIETTA ACQUAH

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BY

HENRIETTA ACQUAH

Thesis submitted to the Department of Chemistry in the School of Physical Sciences, College of Agriculture and Natural Sciences, University of Cape Coast, in partial fulfilment of the requirement for the award of Master of Philosophy in Chemistry

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the results of my own original research and that no part of it has been presented for another degree in the university or elsewhere.

Candidate's signature…… Date……..

Name: Henrietta Acquah

Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

Principal Supervisor's Signature…… Date……

Name: Prof. David Kofi Essumang

Co-supervisor's Signature……. Date……..

Name: Dr. Joseph Adjei

ABSTRACT

The presence of pharmaceuticals and endocrine disrupting compounds in raw water and for that matter treated drinking water has serious health implications. The study sought to investigate the levels and distribution Bis-phenol A, Chloramphenicol,17-alpha-Ethynlestradiol,17-beta-Estradiol, Estrone, Diclofenac Sodium Salt, Primidone, Testosterone, Progesterone, 4-tert-Octylphenol and 4-para-Nonylphenol in raw and tap water from Cape Coast and Takoradi metropolises in Ghana. A total of twenty-six (26) water samples were analyzed in replicates for the selected contaminants. Samples were extracted using SPE and further analyzed UHPLC- UV. Levels of the analytes in raw water ranged from 0.185 µg/L to 21.011 µg/L for samples from Cape Coast and 0.028 µg/L to 3.642 µg/L for Takoradi respectively, whiles levels in tap water ranged from 0.018 µg/L to 12.324 µg/L for Cape Coast and 0.011 µg/L to 2.944 µg/L for Takoradi. Estrone, 4-para-Nonylphenol and 4-tert-Octylphenol had the highest concentration among the eleven (11) compounds. The results obtained implied that conventional water treatment methods may not be enough to remove these contaminates from drinking water, hence tap water is a relevant route for human exposure to pharmaceuticals and endocrine disrupting compounds. Source apportionment revealed four (4) signature sources of the analytes which were attributed dumpsite, wastewater from hospitals, wastewater from homes and veterinary usage.

KEY WORDS

Endocrine Disruptors

Conventional water treatment

Pharmaceuticals

Raw water

Tap water

Waste water

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DEDICATION

In memory of my parents.

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LIST OF ABBREVIATIONS

BWTP	Brimsu Water Treatment Plant
DWTP	Daboase Water Treatment Plant
EDCs	Endocrine Disrupting Compounds
EPA	European Pharmaceutical Agency
GWCL	Ghana Water Company Limited
HPLC	High Performance Liquid Chromatography
LOD	Limit of Detection
LOQ	Limit of Quantification
MLR	Multiple Linear Regression
PCA	Principal Component Analysis
SPE	Solid phase extraction
USA	United State of America
WHO	World Health Organization
WWTP	Wastewater Treatment Plant

CHAPTER ONE

INTRODUCTION

The quality of drinking water is affected by several contaminants usually through human activities. The severity of the problem depends on how much of these contaminants are removed during the treatment of drinking water. Increasing population has led the ubiquitous use of pharmaceuticals and other industrial chemicals which contaminate the aquatic environment. The presence of pharmaceuticals and endocrine disruptors in aquatic environment and consequently drinking water pose a threat to aquatic organisms and public health. A number of studies have identified and quantified several pharmaceuticals and endocrine disruptors in raw, waste, and tap water and the dangers they pose from different part of the world. Policy makers and health organizations need information on the quality of water in any particular location to guide them develop policies that will help maintain or improve the quality of water especially drinking water in that location. This thesis seeks to provide information on the presence and levels of pharmaceuticals and endocrine disrupting industrial chemicals in raw and tap water. Samples of raw water and tap water from different locations within the central and western regions of Ghana. The concentration of these contaminants will somehow asses the efficiency of the methods employed in the treatment of raw water for drinking.

Background to the Study

Pharmaceuticals are a valuable and required component of life. They are used in agriculture, human and veterinary medicine to prevent, cure, treat disease and improve health. (Madikizela et al., 2017, Veiga-gomez et al.;

2017). Upon intake of pharmaceuticals, they are subjected to metabolic breakdowns, including oxidation, reduction hydroxylation, cleavage and glucuronation for maximum effect. However, many pharmaceuticals are not completely metabolized in the body and are therefore excreted after slight transformation or in unchanged form. (Madikizela et al., 2017). Consequently, the rampant usage of pharmaceuticals has led to the gradual release of these compounds, usually at nanograms to low micrograms per liter into the water cycle; including surface water, wastewater and to a lesser extent in drinking water (WHO, 2012).

Clean water is a requirement for good health, human growth and development. Enhancing and guaranteeing people's access to better water supplies is also both a public health initiative and a humanitarian campaign (Agbadi et al., 2019). However, over the last decade, the emergence of pharmaceuticals and endocrine disrupting compounds in the aquatic environment, including drinking water has raised questions about their future effects on public health. High concentrations of these compounds are known to induce harmful effects such as endocrine disruption, neurotoxicity and cytotoxicity (Gou, et al., 2016, Schröder, 2010). But it is not clear what toxicological implications of chronic exposure to trace pharmaceuticals and endocrine disrupting compounds in drinking water may pose and that has drawn concerns from medical professionals, environmental scientists, drinking water municipalities, government agencies, and the general media (Benotti et al., 2009).

There is rising global interest in the presence of pharmaceuticals and endocrine active industrial chemicals in drinking water, therefore, removal of

these compounds in wastewater and source water for domestic water treatment plants are widely studied (Eugenido et al., 2015). However, great discrepancies are observed between countries indicating the regional differences in drug use patterns (Luo et al., 2014, Mailler et al., 2016). Variations are also observed even within the same country between different water sources probably due to the different usage of these compounds and the varied removal efficiencies of individual water treatment plant. (Guerra et al., 2014).

Conventional water treatment methods such as coagulation, sedimentation and filtration have poor removal efficiencies for most pharmaceuticals and industrial chemicals present in water. However, efficiencies of advanced treatment methods like ozonation and granular activated carbon filtration are reportedly higher. (Zhang et al., 2014; Verlicchi and Zombello, 2014).

Statement of the problem

Pharmaceuticals and endocrine disrupting compounds are classified as emerging contaminant of the aquatic environment by the World Health Organization. (WHO, 2012). The most significant entry route for these compounds into aquatic environments is their release from wastewater treatment plants (Lindqvist et al. 2005) et al.; 2002). Also most pharmaceuticals are excreted by stool and urine as a combination of metabolites and substances that mostly remain unchanged in the environment (Bottoni et al., 2010). Furthermore, improper disposal methods such as flushing unused or excess pharmaceuticals and personal care products down

toilets and sinks and discarding them in domestic wastes contribute greatly to the prevalence of these compounds in water (WHO, 2012).

The continuous exposure to pharmaceuticals and endocrine disrupting compounds in tap water by unintended methods over a while could be detrimental to public health. Globally, it has been scientifically demonstrated that most waste water treatment plants (WWTP) are unable to remove the pharmaceuticals completely during the sewage treatment process which led to the contamination of surface water (Sun et al., 2014; Gurke et al., 2015).

In many African communities including Ghana, there are areas where there is poor or no sanitation facilities (Segura et al., 2015). Such areas do not have sewage treatment plants therefore human waste is directly disposed into water bodies aggravating the problem of contamination which is dire to public health. In addition, pharmaceutical contamination in water bodies may lead to drug resistance in both aquatic organisms and humans.

Many research papers have indicated the wide spread of pharmaceuticals and industrial chemicals in aquatic environment (Medikezal et al., 2017). However, most of these scientific papers emerge from the western countries. Africa and for that matter Ghana lacks behind in terms of identifying and quantifying pharmaceuticals and endocrine disrupting industrial compounds in environmental samples.

Purpose of the study

This study aimed to investigate the levels and distribution of selected pharmaceuticals and endocrine disrupting compounds in raw and tap water in some communities within Cape Coast and Takoradi metropolises.

Specific Objectives

The study sought to:

1. Determine the levels of the eleven (11) selected pharmaceuticals and endocrine disrupting compounds in the raw water feeding the Brimsu Water Treatment Plant (BWTP) for Cape Coast and Daboase Water Treatment Plant (DWTP) for Takoradi.
2. Determine the levels of the selected compounds in the tap water delivered from these water plants to ten communities within Cape Coast and Takoradi.
3. Compare concentration levels of the selected pharmaceuticals between raw water and tap water to somehow check the efficiency of the treatment methods available at BWTP and DWTP.
4. Conduct source apportionment to establish source signatures and contributors of these contaminates.

Significance of the study

The treat of pharmaceuticals and endocrine disrupting compounds on aquatic organisms and public health cannot be ignored. However, minimal data are available on the types and concentrations of pharmaceuticals and endocrine active compounds found in tap water supplied by water treatment plants in Ghana. The study seeks to investigate the levels and distribution of pharmaceuticals and endocrine disruptors found in raw and tap water from Cape Coast and Takoradi. Results from this study will add to literature, set the pace for improve treatment process and protect public health.

Delimitations

There are several classes of classes of pharmaceuticals which are used in human and veterinary medicine to treat diseases and improve health, also many endocrine disrupting industrial chemicals are constantly being released into the aquatic environment. Their presence and quantity can be determined using several methods. However, this study will focus on the determination of some selected pharmaceuticals and endocrine disruptors in raw water from selected water treatment plants and tap water provided by these treatment facilities using solid phase extraction and high performance liquid chromatography.

Limitations

Though the tap water sampled from the various communities were treated by the same water treatment plant, the levels of the selected compounds in each sample differed from the other. These differences in concentration of a particular compound in the various tap water samples could not be explained by this study.

Organization of the study

Chapter one presents the general overview of pharmaceuticals and endocrine disruptors in aquatic environment and consequently drinking water. This chapter also gives the problem statement, purpose and significance of the study as well as the scope the limitations of the study. Chapter two gives comprehensive literature on the effects of pharmaceuticals and endocrine disruptors in water, the sources of these contaminants in aquatic environment and groups of pharmaceuticals commonly found in water. This chapter further outlines some analytical methods of analyzing pharmaceuticals and endocrine

disruptors in water. Chapter three outlines the materials and methods employed in the study, as well as details on the study area. Chapter four presents and discusses all results obtained from the study whiles chapter five presents the summary of the study, conclusions drawn from the results obtained and recommendations for further studies.

Chapter Summary

The benefits of pharmaceuticals and certain industrial chemicals were detailed in this chapter Also the threat posed by the presence of these compounds in water especially drinking water were elaborated. Finally, the objectives, significance, delimitations and limitations of the study were also outlined.

CHAPTER TWO

LITERATURE REVIEW

Introduction

With relevant literature, this chapter presents different types of pharmaceuticals and endocrine disrupting compounds in water, their effects and the sources of contamination. It also outlines various techniques used in treating water to remove such contaminants and the analytical methods employed in analyzing these contaminants of water.

Effects of Pharmaceuticals and Endocrine Disrupting Compounds in Drinking Water

The widespread use of pharmaceuticals (both prescribed and over the counter) and household product with endocrine disrupting industrial chemicals has resulted in a relatively continuous discharge of these compounds and their metabolites into wastewater (WHO, 2012). Following advances in the sensitivity of analytical methods for the measurement of these chemicals at very low concentrations, a number of studies have found trace concentrations in wastewater, various water sources and some treated drinking water. Concentrations in surface water, groundwater and partially treated water were typically less than 0.1 µg/L, whereas concentrations in treated water were generally below 0.05 µg/L. (WHO, 2012).

The evidence of adverse effects of pharmaceuticals and EDCs on aquatic organisms at these levels is well documented (Manickum & John 2014). Few studies have attempted to establish human risk assessment by applying the principle of “minimum therapeutic dose”, acceptable daily

intake in conjunction with safety factors or uncertainty factors for different groups of these compounds. (WHO, 2012).

Current observations suggest that it is very unlikely that exposure to very low levels of pharmaceuticals and EDCs in drinking-water would result in appreciable adverse risks to human health, as concentrations detected in drinking-water are several orders of magnitude lower than the minimum therapeutic dose. The extent of exposure to humans has been deemed as negligible in most cases, citing 'no appreciable risk to humans exist'.

However, the concern associated with human exposure to pharmaceuticals and EDCs is mainly based on the following ; observed reproductive irregularities in fishes and aquatic life(Manickum &John,2014), documented clinical cases of cancers related to hormones in industrialized countries as well as prevalence of reproductive disorders in pre-pubertal and adolescents young men in Europe (Cortes Munoz et al.,2014) as well as the uncertainties related to prolong exposure to pharmaceuticals in drinking water still exist and warrant consideration. (Kumar et al., 2009).

Sources of Pharmaceuticals and EDCs in Water

The presence of pharmaceuticals and EDCs in water bodies is due mainly to the discharge of wastewater, Agricultural and Veterinary usage and landfills and sewage disposal sites.

Wastewater effluents

Wastewater effluents are one of the major and longest-standing contributors to the levels of pharmaceuticals and EDCs in water. Wastewater

from industries, hospitals, and municipal wastewater treatment plants have all been shown to contain pharmaceuticals and endocrine active industrial chemicals (Hartmann et al., 1999, Fick et al., 2009, Koplin et al., 2002). It has long been known that even treated wastewater could still contain pharmaceuticals. In 1965, a report by Harvard University's Stumm-Zollinger and Fair showed that hormones were not completely removed after wastewater treatment (Stumm-Zollinger & Fair, 1965). Besides, different wastewater treatment plants have different removal efficiencies (Fernández-López et al., 2916), thus, it is not surprising that the release of "treated water" has the propensity to douse water bodies with pharmaceuticals and EDCs. The contribution of wastewater to the pharmaceutical EDCs contamination of water may even be higher in Africa due to the paucity of proper wastewater treatment systems and the findings of Segura et al. (2015) lends credence to this notion.

Agricultural sites and veterinary usage

The agricultural sector consumes a lot of pharmaceuticals and chemicals with endocrine active compounds. Livestock production and aquaculture constitute approximately 80% of the antibiotics in the United States (Hollis & Ahmed, 2013). A significant portion of livestock antibiotics is used for non-therapeutic purposes i.e., growth promotion. Such pharmaceuticals may end up in the soil through animal excreta as manure (Awad et al., 2014) or when the animals die and are buried in the earth (Yuan et al., 2013). Antibiotics and other chemicals are sprayed on plants to prevent diseases. These may also be washed off when it rains and end up in water bodies.

Landfill and sewage disposal sites

In most countries, most of the solid waste generated goes to landfill sites and pharmaceuticals are no exception. Once solid waste (pharmaceuticals included) is deposited at the landfill site, it may either be degraded or end up in leachates (Sui et al., 2015). Several drugs have been isolated from landfill leachates including, carbamazepine, ibuprofen, diclofenac, acyclovir and ganciclovir (Eggen et al., 2010; Peng et al., 2014). Holm, et al (1995), found pharmaceuticals in groundwater proximal to a landfill site in Denmark, thus, reinforcing the idea that pharmaceuticals in leachates may either be washed into surface water as run-off or may leach into groundwater and contaminate it. In the case of groundwater, the anaerobic conditions that come into play may lower the rate of biodegradation and increase pharmaceutical persistence (Erses et al., 2008).

Factors that Influence the Persistence of Pharmaceuticals and Endocrine disrupting Compounds in Water

Water source

For the production of drinking water, two main sources of water are considered: surface and groundwater. Both sources of water are contaminable however, it is generally accepted and known that surface water has a higher likelihood of being contaminated with pharmaceuticals and then groundwater, due to its relatively exposed nature. For example, Fick and colleagues (2009), found high concentrations of pharmaceuticals in the investigated surface water and wells in a pharmaceutical industrial area in India, however, despite the high concentrations of pharmaceuticals observed in general, there were marked differences between surface and groundwater contamination levels

(Fick et al., 2009). Additionally, the aerobic nature of surface water may positively affect degradation rates by aerobic organisms (Sui et al., 2015). The relative paucity and reduced diversity of microorganisms in groundwater when compared to surface waters, and anaerobic conditions may prolong the persistence of biodegradable pharmaceuticals in groundwater.

Resistance to degradation

Pharmaceuticals like other substances are also susceptible to degradation, thus the longer a pharmaceutical or steroid can resist degradation, the longer it can persist in water. Degradation in this context includes biodegradation (degradation by microbes), hydrolysis and photolysis, however, pharmaceutical products are usually capable of withstanding hydrolysis (Nikolaou et al., 2007). Different pharmaceuticals are degraded differently under different conditions and rates (Loftin et al., 2008). Antibiotics, in general, may resist biodegradation due to their anti-microbial activity which may suppress the growth of bacteria and their downstream degradative capabilities. Also, other physicochemical properties of the pharmaceutical may interfere or aid the degradative process. For example, 4-quinolone antibiotics are strong soil absorbers hence, they can be hard to degrade. Some bacteria such as *Rhodococcus zopfii* and, *Rhodococcus equi* have been found capable of degrading some oestrogens into harmless products (Jjemba, 2018). Abiotic degradative processes like photolysis can also contribute to the degradation of pharmaceuticals, and even under experimental conditions, Andreozzi et al., (2006) demonstrated the photo-degradability of lincomycin.

Physicochemical properties

Different chemicals have different physiochemical properties and by extension, so do pharmaceuticals. These physicochemical properties confer the therapeutic and medicinal properties upon the various pharmaceuticals. However, beyond the therapeutic uses of the drug, the physiochemical properties of pharmaceuticals are major determinants in its fate or persistence in the environment (Jjemba, 2018). Sorption, mobility, degradation (bio or abiotic), complex formation etc. are all determined either directly or indirectly by the physicochemical properties. For instance, soil sorption of pharmaceuticals, among other things, depends on the octanol-water partition coefficients (K_{ow}), ionisation constant (pK_a) and speciation (be it negative, neutral, zwitterionic or positive) of the active pharmaceutical ingredients (Aga, 2007). With regards to steroids, Lai et al. (2000) reported that estrogen sorption to the soil, increased with increasing hydrophobicity, as indicated by K_{ow} values: mestranol > ethinylestradiol > estrone > estriol . Furthermore, the successful removal of steroid or hormone by ozonation during water treatment may depend on the presence or absence of a phenolic or aromatic moiety (Westerhoff et al., 2005). Thus, the physicochemical properties of a pharmaceutical or steroid may affect its ability to "survive" the drinking water treatment process.

Conventional water treatment process and the fate of pharmaceuticals

Drinking water treatment involves processes used to manipulate water obtained from various sources into that which is free from microbes and harmful chemicals. There are minor differences in the water treatment process used by different drinking water treatment plants, however, the key processes

employed bare: aeration, clarification (coagulation, flocculation, sedimentation, filtration) and disinfection (chlorination, ozonation or Ultraviolet radiation) (WHO, 2012).

Aeration

During aeration, air-water is brought into close contact with air. This helps remove dissolved gasses, volatile compounds and metals. The metals are oxidized into insoluble forms that can then be removed by other processes (MRWA, 2011).

Coagulation, flocculation, sedimentation and filtration

Coagulation in water treatment involves the addition of coagulants (Common examples of coagulants are: Aluminum Sulfate, Ferric Sulfate, and Ferric chloride) which produce positive charges in water to neutralize the negatively charged colloids that reduce the clarity of the water. The neutralization of the negative charge allows the colloids to aggregate into micro flocs (Ives, 2018). It is from this point onward that the flocculation process is brought into play. Flocculation involves a gentle agitation of the water that increases the chances of collision between the micro flocs. (Fig.1). The accumulation of micro flocs into bigger and heavier flocs which can then be removed by gravity (sedimentation) (Safe Drinking Water Foundation, 2017) or filtration which involves the removal of colloids and other turbidity-causing substances by trapping them based on their size.(Fig.1) Sand is one of the most commonly employed mediums for filtration. Recently, however, the use of membranes for filtration is becoming increasingly common leading to filtration processes such as ultra-filtration and microfiltration.(Singley, Robinson, & Updated by Staff, 2006).

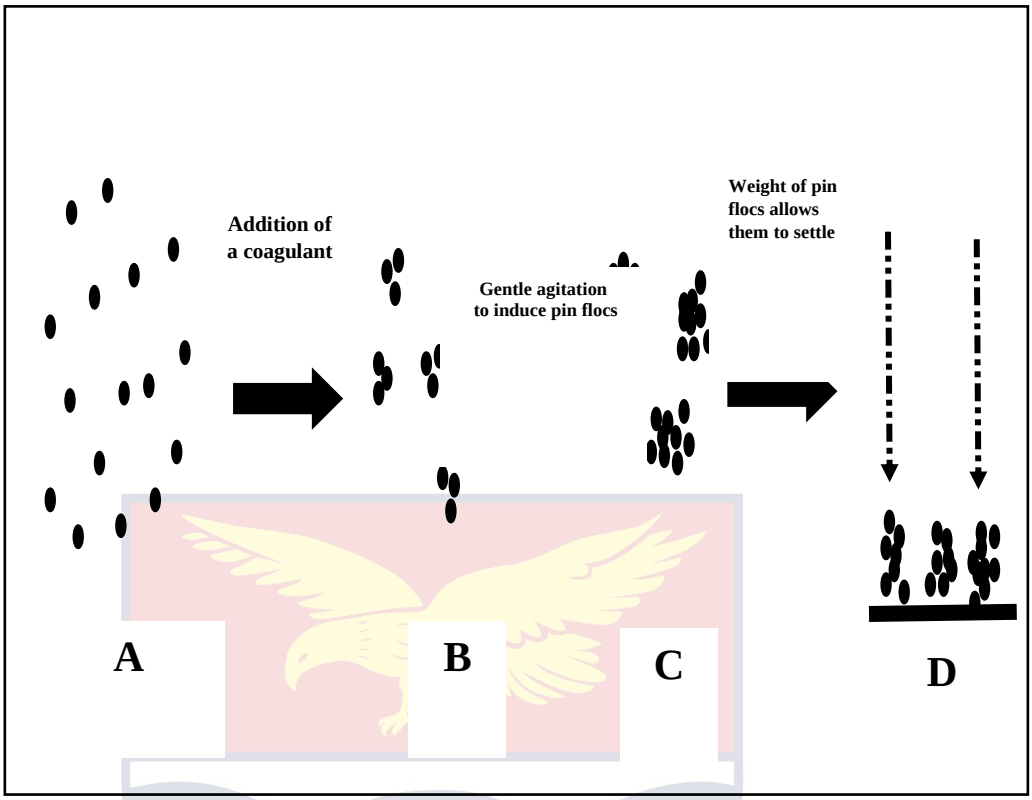


Figure 1. Coagulation, flocculation, sedimentation and filtration

Disinfection

This process in water treatment traditionally involves the addition of chlorine to kill microbes present in the water, hence, it is also sometimes called the chlorination step. It can be done both as the first step and/or the last step in water purification. Some drinking water treatment plants have substituted chlorine for ozone and others supplement it by adding an ultraviolet radiation step (Safe Drinking Water Foundation, 2017).

Drinking water treatment and pharmaceutical removal

The processes of clarification (coagulation, flocculation, sedimentation and/or filtration) do not significantly contribute to pharmaceutical removal (Adams et al., 2002). However, some pharmaceuticals may be removed due to their ability to sorb on to particulate matter that may be removed during the clarification process (Westerhoff et al., 2005). Conversely, the disinfection

processes seem to have higher pharmaceutical removal efficiency. Chlorination is useful in the removal of sulfonamides, fluoroquinolones and analgesics and anti-inflammatories; however, it is unsuitable for the removal of erythromycin, carbamazepine, caffeine, or cotinine (Gibs et al., 2007). Ozone is a powerful oxidant that can remove pharmaceuticals from water either through oxidation by molecular ozone or the generation of free radicals. Snyder et al., (2006), reported more than 80% decrease in the concentration of acetaminophen, carbamazepine, diclofenac, erythromycin, gemfibrozil and trimethoprim after treatment with ozone. Even though the removal rates of disinfection processes in conventional water treatment supersede that of the clarification processes, they are not absolute, and some pharmaceuticals may persist.

Classes of Pharmaceuticals commonly found in water

Numerous pharmaceuticals belonging to various pharmaceutical classes- have been detected in surface, ground and drinking water. Four classes of pharmaceutical most commonly found in water are Antibiotics, Analgesics and anti-inflammatories, Steroids and Hormones and Lipid regulators.

Antibiotics

Antibiotics are one of the most widely used class of pharmaceuticals. Approximately 5460 tons of antibiotics are used by the European Union per year (Hu et al., 2018). Antibiotics are prescribed not just for human use but for veterinary purposes too. They are of paramount concern due to their potential to promote the growth of antibiotic-resistant microbes. Surface waters and sewage effluents in the United States and Europe have been found to contain

sulfonamides, fluoroquinolones, tetracyclines, macrolides, chloramphenicol and trimethoprim (Monteiro & Boxall, 2010). Fick et al., (2009), also found high levels of fluoroquinolones in both groundwater and surface water in India. Antibiotics have also been reported in drinking water in Spain (Hu et al., 2018), Italy (Perret et al., 2006) and China (Ben et al., 2020). There are instances where metabolites and degradation products of the drugs were rather identified such as acetylsulfamethoxazole, a metabolite of sulfamethoxazole (Ashton et al., 2004) and dehydro-erythromycin, a degradation product of erythromycin (Hirsch et al., 1999).

Analgesics and anti-inflammatories

Analgesics and anti-inflammatories are colloquially called pain-killers. A significant number of the members of this class of drugs that end up in the water are Non-steroidal anti-inflammatory drugs. They have been widely detected in sewage treatment effluents and surface waters in the West, with ibuprofen, diclofenac, acetaminophen and naproxen being the common culprits (Monteiro & Boxall, 2010). Analgesic metabolites such as acetylsalicylic acid (a metabolite of aspirin) was detected in Spanish surface waters by Farré and colleagues (Farré, et al., 2001). Ibuprofen, diclofenac, naproxen, and ketoprofen are also quite common in the African aqueous ecosystem (Madikizela, Tavengwa, & Chimuka, 2017). Groundwater has not been spared from analgesic and anti-inflammatory contamination either, with acetaminophen and diclofenac being detected in identified in the Mediterranean region (Rabiet et al.,2006) and phenazones being detected by Redderson and colleagues in Germany (Reddersen, Heberer, & Dünnbier, 2002). Redderson et al., (2002) went on to find 1-acetyl-1-methyl-2-dimethyl-

oxamoyl-2-phenylhydrazide (AMPDOH), an oxidation product of dimethylaminophenazone, in German drinking water albeit at lower concentrations than allowable concentration level of 3 mg/L recommended by the Federal Environmental Protection Agency (Reddersen, Heberer, & Dünnbier, 2002).

Steroids and hormones

Steroids are an important class of water contaminant due to their ability to affect or influence reproductive and endocrine systems. Such effects are not limited to just humans and aquatic organisms such as fish can be affected (Jobling et al., 1998). In the US, a national reconnaissance performed in 2002, reported the occurrence of various reproductive hormones, ovulation inhibitors and steroids in US streams (Kolpin, et al., 2002).

Hohenblum et al., found hormones in surface and groundwater (Hohenblum, et al., 2004). In South Africa, estrone, 17-b-estradiol, 17-are ethinylestradiol, progesterone, estriol and testosterone were detected in rivers and water entering and existing wastewater treatment plants. The steroid and hormone levels in the river were generally low (Manickum & John, 2014).

Lipid regulators

Lipid regulators are usually categorized into two groups; statins and fibrates, both of which are used to decrease the levels of cholesterol and triglycerides. Members of this class of pharmaceuticals, bezafibrate and gemfibrozil to be specific were detected in high frequencies in Spanish groundwater (López et al., 2013), and in low detection frequencies in China (Tong et al., 2014) and Singapore (Tran et al., 2014). Surface waters have also been found to contain clofibric acid, a metabolite of clofibrate (Calamari et al.,

2003; Thomas & Hilton, 2004; Tixier et al., 2003). Atorvastatin, one of the highest prescribed drugs in the US, was found in 3 out of the 19 sources of water. (Benotti et al., 2009).

Endocrine Disruptors Found in Water

In recent years concern has been raised about the possibility that reproductive disorders reported in humans and wildlife populations might stem from exposure to substances present in the environment which mimic estradiol, the so-called endocrine disrupting compounds (Hejmej et al., 2011). These compounds include Bis-phenol A, 4-tert-octylphenol and 4- para-nonylphenol. Bis-phenol A is a synthetic compound used in the manufacture of polycarbonate plastics such baby feeding bottles, re-useable water bottles tableware and as coating for food can lining to extend shell life.4-tert-octylphenol is used as a plasticizer, fuel oil as well as in the manufacture of fungicides and disinfectants. 4-para-nonylphenol is used in the manufacture of antioxidants, lubricating oils, detergents, emulsifiers and in personal care products. The ubiquitous usage of these chemicals ensures their prevalence in the environment. Exposure to chemicals with estrogenic activity may have potential to adversely affect the endocrine system and reproductive organs in males and females. Thus, the presence of these chemicals in water has become a public health concern (Smarr et al, 2016). Exposures to Bisphenol A is known to reduce fertility in mammals by prematurely activating primordial follicles and altering levels of sex-steroid hormones (Patel et al., 2017). In some provinces of South Africa, Bis-phenol A was found to be present in 62% of the analyzed drinking water and wastewater samples ((Hejmej et al., 2011). Also, a study in France determined Bis-phenol A levels of 1430 ng/L and

between 9 to 50 ng/L, in raw and tap water samples respectively. Studies on the exposure of U.S. population to 4-tert-octylphenol revealed that this compound was present in the urine of 57% of persons >6 years of age with total concentrations ranging from 0.2 g/L to 20.6 g/L (Calafat et al., 2008). Currently, 4-tert-octylphenol has been also found in human breast milk (Ademollo et al., 2008). 4-tert-octylphenol can affect invertebrates, amphibians and fish. (Evans et al., 2011).

Analytical Techniques for Analyzing Pharmaceuticals and Endocrine Disruptors in Water

Methods applied in the analysis of pharmaceuticals and endocrine disrupting compounds in water are based on solid phase extraction (SPE) with chromatography (liquid or gas) coupled with mass spectrometry or tandem mass spectrometry. The European Pharmaceuticals Agency (EPA) recommended the Method 1694 for the determination of 70 pharmaceuticals divided into four groups: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment, and Bio solids by HPLC/MS/MS (Ferrer et al., 2010). Gros at al., (2012) used SPE-UPLC-MS/MS, to analyze different classes of pharmaceuticals and some of their metabolites in tap water. Solid phase extraction (SPE) and High performance liquid chromatography (HPLC) were the analytical technique used in this study.

Solid Phase Extraction (SPE)

SPE method is used in the extraction of pharmaceutical and other industrial chemicals from water for the following reasons; compatibility of the sorbent and analytes is high and can be modified by varying the pH of the sample and the type of sorbent. SPE sorbents have universal sorption potential therefore different types of analytes required for multi-analysis are able to be extracted. Also, the sequential elution of neutral, acidic and basic analytes is possible. Finally, a very high concentration factor can be achieved which in trace analysis is essential. SPE cartridges most often used for extraction of pharmaceuticals from drinking water have great lipophilic-hydrophilic balance to ensure the extraction is non-selective and perfect for multi-analysis**.** (Boleda et al., 2013). SPE is used most often to prepare liquid samples and extract semi volatile or nonvolatile analytes, but also can be used with solids and can be automated as well to save time. The C-18 bond elute is the most hydrophobic bonded silica.it has the broadest retention spectrum among bonded silica bonded sorbents. It retains most organic analytes from aqueous matrix. SPE uses the principle of portioning of compounds between two (2) phases of solid and liquid. It involves adsorption of analytes from liquid matrix onto solid sorbent and subsequent elution of the analytes from the sorbent into an organic solvent that may be injected for analysis by HPLC. (Li et al., 2006)

High performance Liquid Chromatography (HPLC)

HPLC is a form of column chromatography that pumps analytes in a solvent (known as the mobile phase) at high pressure through a column with chromatographic packing material (stationary phase). The sample is carried by

a moving carrier gas stream of helium or nitrogen. HPLC has the ability to separate, and identify compounds that are present in any sample that can be dissolved in a liquid in trace concentrations as low as parts per trillion. Sample retention time vary depending on the interaction between the stationary phase, the molecules being analyzed, and the solvent, or solvents used. As the sample passes through the column it interacts between the two phases at different rate, primarily due to different polarities in the analytes. Analytes that have the least amount of interaction with the stationary phase or the most amount of interaction with the mobile phase will exit the column faster. Main components in an HPLC system include the solvent reservoir, or multiple reservoirs, a high-pressure pump, a column, injector system and the detector. The reservoir holds mobile phase and the pump generate a specified flow of the mobile phase. The injector or auto sampler introduces the solvent into a phase stream that carries the sample into the high pressure column which contains specific packing material (stationery phase) needed to effect the separation. The detector "see" the separated compound bands as they elute from the high pressure column. The information is sent from the detector to a computer which generates the chromatogram. The mobile phase exits the detector and is either sent to a waste, or collected, as desired.

Chapter Summary

This chapter discussed the different kinds of pharmaceuticals and endocrine disruptors found in water and their potential threat to aquatic life and public health. It also elaborated the various methods applied in treatment of water and their ability to remove these contaminates from drinking water.

The chapter further outlined some common analytical methods employed in identifying and quantifying the compounds in water samples.

CHAPTER THREE

METHODOLOGY

Introduction

This chapter sets out details on how the study was conducted. It presents the study area, sample collection and preparation as well as the steps involved in all the analytical procedures performed to provide data on pharmaceuticals in drinking water in some communities within Cape Coast and Takoradi, in the Central and Western Regions of Ghana.

Study Area

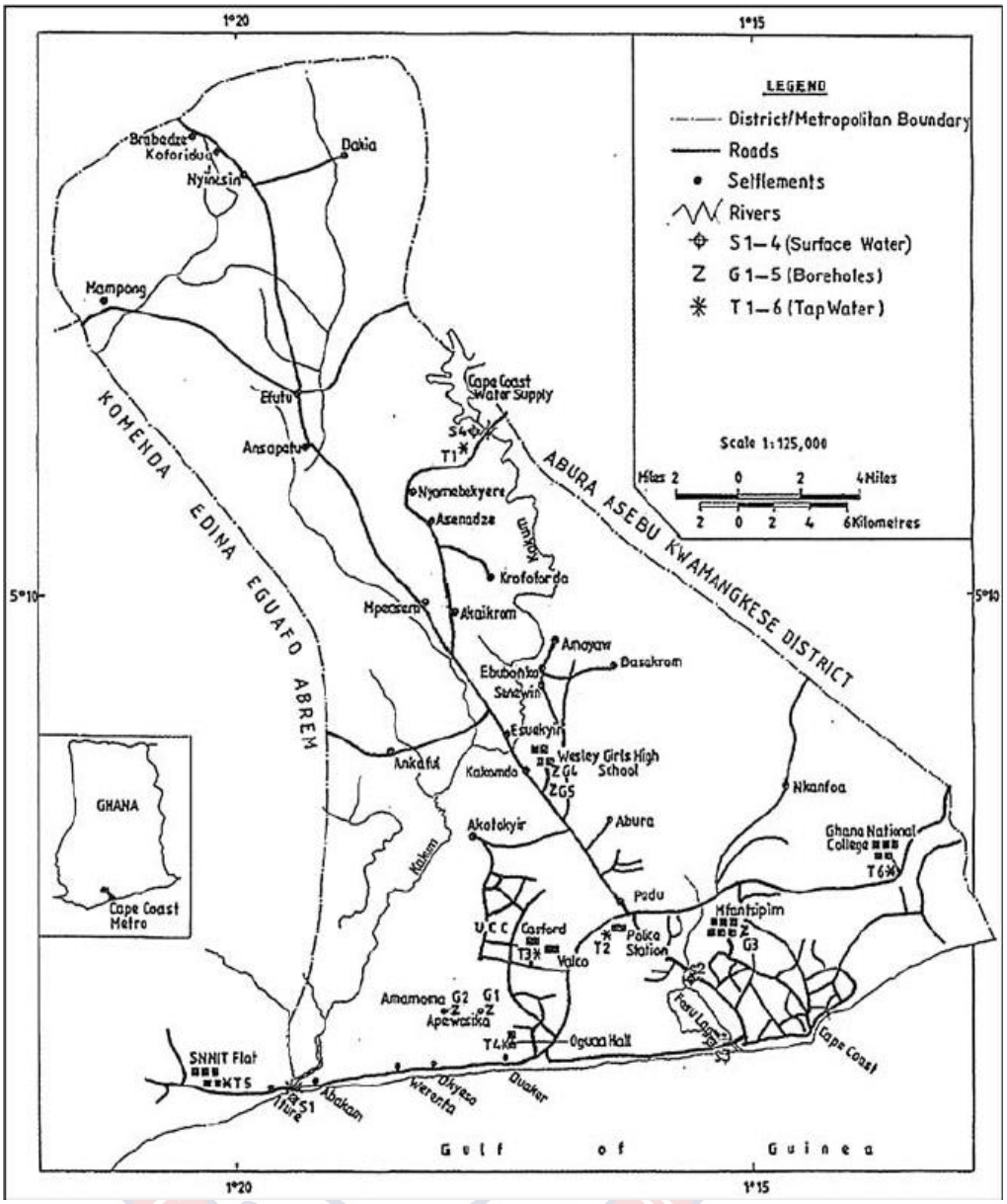
The choice of study area was based on the tendency for unsustainable practice of discharge of wastewater from sources other than pharmaceutical industries. Barring any natural phenomenon as well as human accident to any medical facility in the areas chosen, the more cosmopolitan area should have more pollutants in its water sources than a less cosmopolitan area. By this, Takoradi metropolis which have more medical facilities and household activities compared to Cape Coast metropolis should have more pharmaceuticals in its water. Sampling site for drinking water were spatially distributed throughout the two (2) metropolises chosen for the study.

Cape Coast, the capital city of the Central Region of Ghana has a population of 169,884 and more (2010 census). Being a cosmopolitan, households and other users of portable water primarily depends on the Brimsu Water Treatment Plant (BWTP) situated at Brimsu in the northern part of the Cape Coast metropolis. Taking its source from the Kakum River, BWTP pumps out treated water of an estimated volume of four (4) million gallons daily, for the metropolis and beyond (GWCL).

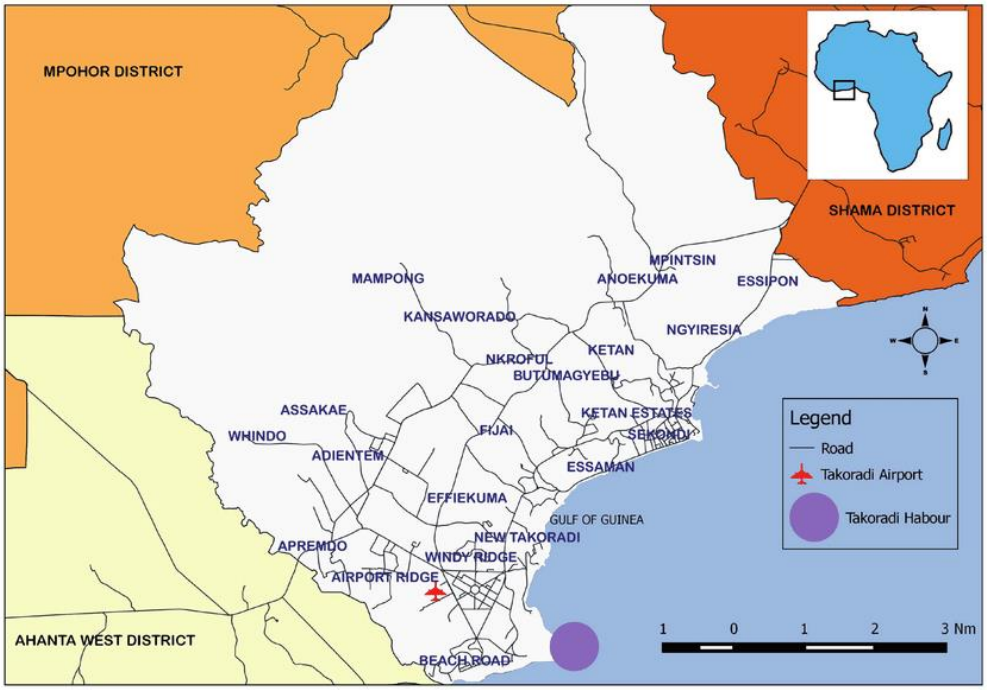
A notable percentage of waste water emanating from human activities which includes health, households and others within Cape Coast and its environs get their way into the Kakum River as pollutants due to improperly regulated waste discharge, treatment and management system.

Ten (10) communities from the north to the south of Cape Coast metropolis were selected for this study. They were Mempeasem, Abura, OLA, Royal Lane Abease, 4th Ridge, Brabedze, Pedu village, CP bus stop, and Amisano

Takoradi, a more cosmopolitan area with vibrant economic activities, and a twin capital of the Western Region of Ghana, gets its treated water from Daboase Water Treatment Plant (DWTP) situated at Daboase in the Mpohor Wassa District of the Western Region of Ghana. Taking it source from the Pra River, the Daboase Water Treatment Plant (DWTP) is estimated to pump out six (6) million (but currently pumps 4.0 million gallons due to mining activities on and along the river banks) gallons of treated water daily for Takoradi and some areas of the Western Region (GWCL/western-region). With a population of 445,205 (www.populationstat.com.gh), Takoradi's only source of treated drinking water is from DWTP, and this supply feeds all households, industries, medical facilities among others. Due to the absence of properly regulated sewage treatment systems within and outside of the area of the water source, and the treatment plant, waste water from human activities mostly finds their way into the Pra River.Ten (10) communities within Takoradi namely Amanful, Efiakuma, Nkruful, Anaji, Kansakorado, Kwesimintsim, Fijai, Tankrom, Assakai and Ntankoful were selected for this study.



Figue 2. Map of sampling area in Cape Coast



Figue 3. Map of sampling area inTakoradi

Chemicals and Materials

Two hundred microgram per litre (200µg/L) steroids and mixed pharmaceuticals standard mix was purchased from Restek Corporation USA. The components were; Bisphenol A, Diclofenac sodium salt, 17-beta-estradiol, 17-alpha-Ethynlestradiol, 4-para-nonylphenol, 4-tert-octylphenol, Primidone, Progestrone and Testosterone. Twenty (20) ppm Chloramphenicol standard from Restek was also utilized. HPLC grade methanol and acetonitrile manufactured by Millipore sigma Germany, analytical grade hydrochloric acid and phosphoric acid of purity 99.9% from KOSDAQ listed company Korea, Agilent HF bond elutC18 cartridges (500mg/6ml) from Agilent Technologies United State of America (USA), MilliQ ultrapure deionised water (R=18.2MΩ) was used throughout.

Sample Collection

A total of twenty-six (26) samples - including three (3) raw water samples each from the dams at Brimsu and Daboase water Treatments Plants, and ten (10) tap water samples from each of the ten (10) communities within each metropolis whose drinking water is supplied by the two water treatment plants were collected within three (3) weeks in August, 2020. Samples were collected in duplicate into plastic bottles pre – washed with 0.1% nitric acid. At the site of collection, the bottles were again washed 3 times with the water before filling them to the brim and labelled. The sample were transported in thermo-insulated boxes to the laboratory kept at room temperature and extracted within 2 weeks.

Analytical Methods

Solid-phase extraction (SPE)

The solid phase extraction was done according to EPA method 1694. The Agilent HF Bond Elute C18 Cartridges were pre-conditioned before use by adding 10 mL methanol followed by 6.0 mL 0.05 N (pH=2.0) HCl (aq). One (1) litre each of all samples (including spiked reagent blank samples) were loaded directly onto the cartridges with delivery tubes at a flow rate of 20 mL/min using Vacuum Extraction Manifold and allowed to dry under vacuum for 5 minutes. Cartridges were then washed with 10 mL 0.05 N (pH=2.0) HCl (aq) and dried for 5minutes under vacuum. A total of 9 ml methanol in quantities of 3 ml portion at a time was used to elute the analytes into glass bottles. The extracts were concentrated to dryness under gentle flow of nitrogen gas, and reconstituted with 1.0 ml acetonitrile. The extracts were then

transferred into vials using syringe disk. The vials were wrapped with aluminum foil stored under room temperature and analyzed within a week.

High performance liquid chromatography (HPLC)

Shimadzu UFLC with LC high gradient pump system (20AD), auto sampler degasser, oven, uv-vis detector and fluorometric (RF) detector was used with the following operating conditions:

Oven temperature: 40.0^{o}c

UV-Vis dual detection wavelength: 222 nm, 256 nm

The compounds were analyzed using EPA method 1694 with slight modification for optimization.

Mobile phase A was 0.14% aqueous phosphoric acid. Mobile phase B was 100% acetonitrile. The flow rate was 0.8 mL/min. the injection volume of both standard and samples was 5 µL, onto the C18 Luna column (4.6 mm x 150 mm) from Phenomenex for the chromatography. The analytes were separated by gradient elution and identified by comparing the retention times and area signals produced to retention times and reference signals for standards acquired under the same conditions. The concentration of each analyte is determined using the integrated peak area and external standard technique.

Analytical Quality Control

To optimize the analytical method, certain quality control measures were taken to check; contamination during sample preparation, reproducibility of the method and the efficiency of the equipment. Six (6) point calibration curves for the selected pharmaceutical standards in concentrations ranging from 0.01 – 7.5 ng/L using linear regression, were used for quantification. Method blank sample was analyzed prior to batch sample analysis.

System suitability

The instrumental method was tested to check its reliability in taken data for both samples and standards. A system suitability test was carried out to check resolution, retention time, pressure, column efficiency and repeatability, plate number, tailing factor and signal-to-noise ratio USP criteria.

Limit of detection (LOD) and limit of quantification (LOQ)

The minimum amount that can be detected as well as the minimum amount that can be quantified of all analytes in the samples were determined and reported using the least amount of the solvent and spiked reagent blank.

Recovery

To determine the recovery percentage of the method, 3 samples (20%) of 1.0 L ultra-pure water were spiked with known concentrations of standard mix and taken through SPE and HPLC analysis under the same conditions as the study samples (EPA method 1694). The recovery percentage was determined by dividing the spiked amount by the recovered amount and multiplying by 10.

Statistical Analysis

Results obtained from the HPLC were analyzed with the following statistical tools; Microsoft excel to determine the arithmetic mean concentration and of each analyte as well as the standard deviation.

IBM SPSS statistics version 22 to conduct source apportionment by principal component analysis and multiple linear regression (APCA-MLR).

Chapter Summary

This chapter detailed how the study was conducted. It elaborated on the study areas, sampling procedures and how the samples were analyzed and explained the various quality control measures taken to ensure method efficiency.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

The main aim of the study is to determine levels of some selected pharmaceuticals and endocrine disruptors in raw and tap water from different communities within the Cape Coast and Takoradi Metropolises. Samples of raw and tap water were analyzed for the concentrations of Bis –phenol A, Chloramphenicol, 17-alpha-ethynylestradiol,17-beta-estradiol, Estrone, Diclofenac sodium salt, Primidone, Testosterone, Progesterone, 4-tert-octylphenol and 4-para-nonylphenol using solid phase extraction and high performance liquid chromatography. This chapter presents and discusses results obtained from all analytical methods employed to achieve the aim of the study.

Calibration curves

The calibration curves obtained for the analysis gave very good fit (R^2 > 0.99) between peak areas. Good response factors percent relative standard deviations (RF %RSD) were obtained for the eleven (11) analytes and were within the acceptance criteria for EPA method 1694 of RF%RSD < 35. 17-beta-Estradiol had RF%RSD of > 35, which is accepted using the calibration curves'R^2 > 0.99. Figures 2 and 3 shows the calibration curves of Bis-phenol A and Chloramphenicol respectively.

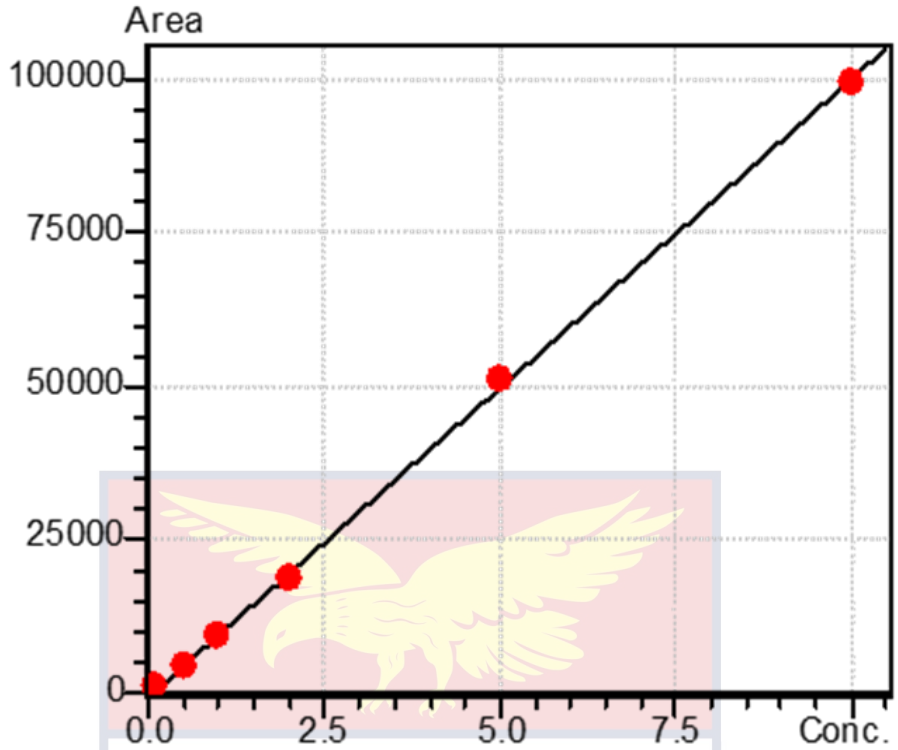


*Figure 4.*Calibration curve for Bisphenol A.

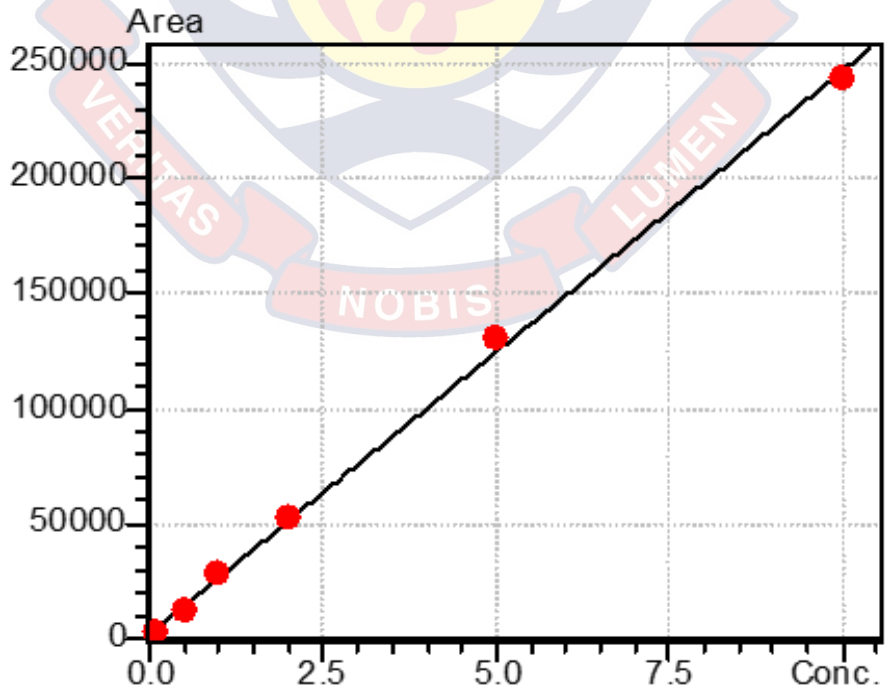


Figure 5. Calibration curve for Chloramphenicol

Limit of detection (LOD) and limit of quantification (LOQ)

Table 1 summarizes the LOD and LOQ of all the eleven (11) selected pharmaceuticals. LOD for the pharmaceuticals ranged from 0.01 to 0.013 ng/L whiles the LOQ was 0.02 to 0. 39 ng/L.

Table 1: Limit of Detection and Limit of Quantification for the Analyte in ng/L

Analyte	LOD	LOQ
Bis - phenol A	0.07	0.20
Chloramphenicol	0.02	0.07
17 - Alpha – Ethynylestradol	0.02	0.07
17 - Beta – Estradiol	0.06	0.17
Estrone	0.07	0.21
Diclofenac Sodium Salt	0.01	0.02
Primidone	0.06	0.18
Testosterone	0.03	0.10
Progestrone	0.08	0.24
4 - tert - octylphenol	0.05	0.16
4 - para - nonylphenol	0.13	0.39

Source: Field work 2020

Recovery studies

Reproducibility and repeatability of the method of analysis was tested by evaluating analyte recovery with spiked ultrapure water. Recoveries were within the acceptance criteria for acid extruded analytes for EPA method 1694 (48.26-150%). 17-Alpha-Ethynylestradiol had the highest recovery followed

by Progesterone and Estrone. Table 2 presents the recovery of the selected pharmaceuticals analyzed in the study.

Table 2: Percentage Recoveries of the Pharmaceuticals from the spiked Ultrapure Water

Analyte	Recovery Percentage
Bis-phenol A	88.90
Chloramphenicol	70.00
17-alpha-Ethynylestradiol	94.28
17-beta-Estradiol	70.85
Estrone	93.90
Diclofenac sodium salt	58.04
Primidone	87.85
Testosterone	86.53
Progesterone	93.56
4-tert-Octylphenol	52.80
4-para-Nonylphenol	83.10

Source: field work 2020

Occurrence of the Selected Compounds in Cape Coast

Chloramphenicol, 17-beta-Estradiol, Estrone, Diclofenac sodium salt, Primidone, Testosterone, Progesterone, 4-tert-Octylphenol and 4-para-Nonylphenol were detected and quantified in all raw water samples at concentration levels ranging from 0.190 to 21.011 µg/L. 17-alpha-Ethynylestradiol was detected in two (2) raw water samples whiles Bis-phenol A, was detected in a single raw water sample at a level of 0.417 µg/L. While

the levels of some of the pharmaceuticals were below detection limit in some tap water samples, Estrone, Testosterone, 4-tert-Octylphenol and 4-para-Nonylphenol were detected in all tap water samples. Estrone recorded the highest concentration levels in most samples followed by 4-para-Nonylphenol. Figures 5 and 6 present mean concentrations of the analytes obtained from the HPLC analysis. In samples where analytes concentration levels were below detection limits, half the LOD was recorded for statistical purposes. The concentration of Bis-phenol A in samples from Amisano (1.737 µg/L) and CP (0.476 µg/L) were elevated compared to 0.417 µg/L in the raw water sample, probably due to cross contamination during distribution. However, concentration of Bis-phenol A in the eight (8) other tap water samples were lower than 0.417 µg/L. Chloramphenicol levels in the three (3) raw water samples were 0.219 µg/L, 0.504 µg/L and 0.345 µg/L whiles the levels in the tap water samples ranged from 0.032 to 0.201 µg/L indicating some degree of removal after treatment. Meanwhile there was no appreciable change in the levels of 17-alpha- Ethynylestradiol in both raw and tap water samples.

17-beta-Estradiol levels in the tap water samples were lower than levels in the raw water which may also be due to efficient removal of this pharmaceutical by the treatment methods employed. Estrone levels in the raw water ranged from 3.04 to 21.011 µg/L whiles levels in the tap water samples ranged from 0.268 µg/L to 12.324 µg/L with Royal lane Abease recording the least, and Pedu village the highest. Mempeasem which is the closest community to the BWTP recorded Estrone concentration of 11.089 µg/L. These elevated levels of Estrone in both raw and tap water maybe an indication of high pollution of the source water and inefficiency of the treatment method in removing

Estrone. Diclofenac sodium salt in the tap water from Brabedze was elevated as compared to concentrations recorded in the three (3) raw water samples. Meanwhile Diclofenac sodium salt levels in all the other tap water samples were lower than levels recorded by the raw water samples.There were elevated levels of 4-para-Nonylphenol in tap water samples from Abura, Babedze, Mempeasem, Ola, Pedu village and Royal lane compared to levels in the raw water samples this may also be due to reasons stated earlier on cross contamination during distribution.

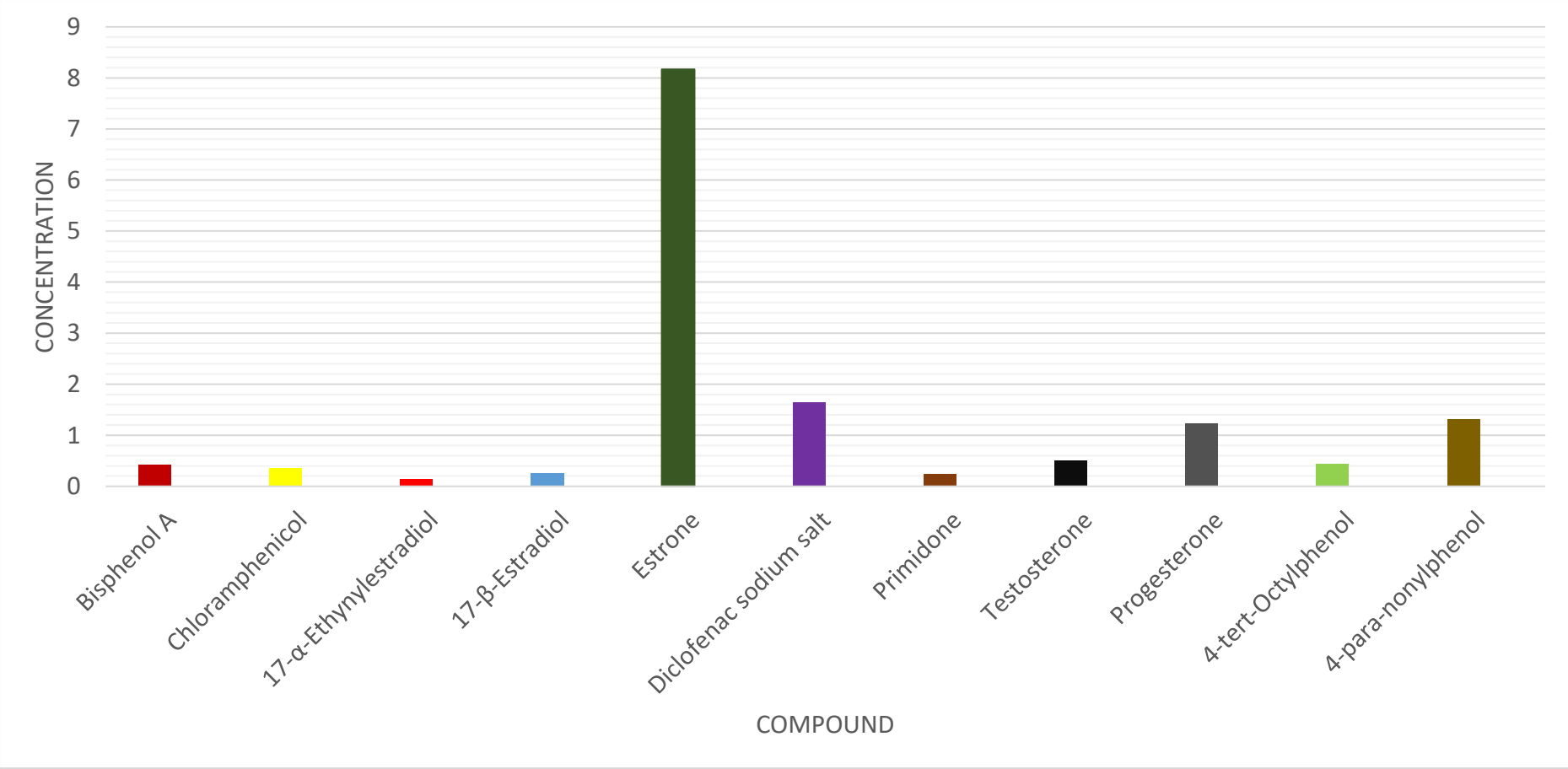


*Figure 6***.** Mean concentration (µg/L) of analytes in raw water from BWTP dam Cape Coast.

Source: Field Work (2020).

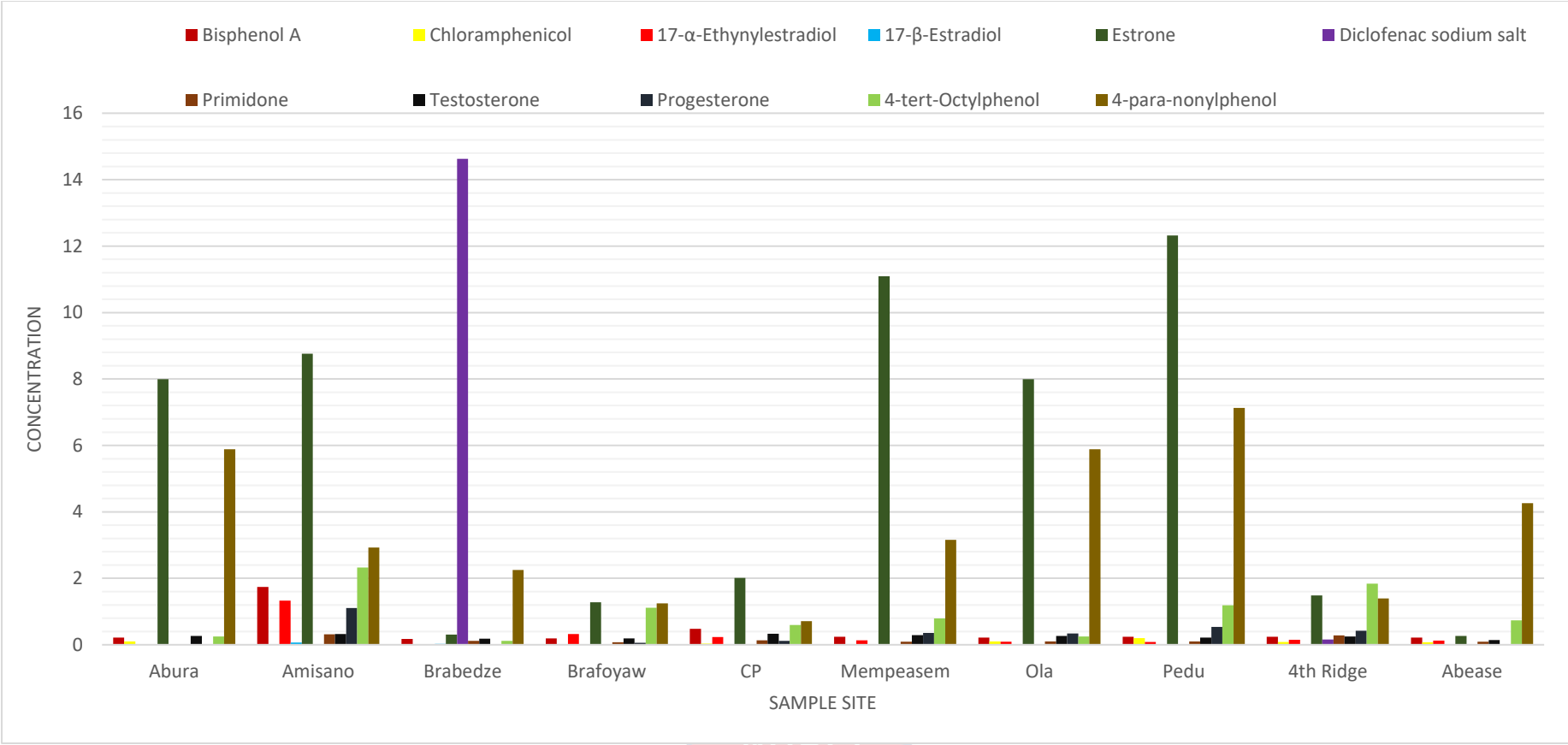


Figure 7. Mean concentration (µg/L) of analytes in tap water from ten (10) communities within Cape Coast.

Source: Field work (2020)

Occurrence of the selected Compounds in Takoradi

All eleven (11) analytes were detected and quantified in all the raw water samples, at levels ranging from 0.028 to3.642 µg/L. Estrone levels in the raw water ranged from 2.922 to 3.642 µg/L the highest among the selected compounds. Its levels in the tap water samples also ranged from 0.119 to1.362 µg/L indicating a probable reduction in levels after treatment. Primidone levels in the three (3) raw water samples (Fig.7) was 0.29 µg/L whiles levels in the tap water ranged from 0.028 to 0.285 µg/L. Diclofenac sodium salt levels in raw water ranged from 0.074 -0.234 µg/L, however levels in tap water samples were below the detection limit (Fig.8). This may be due to efficiency of the treatment process employed by GWCL at DWTP in removing these compounds.

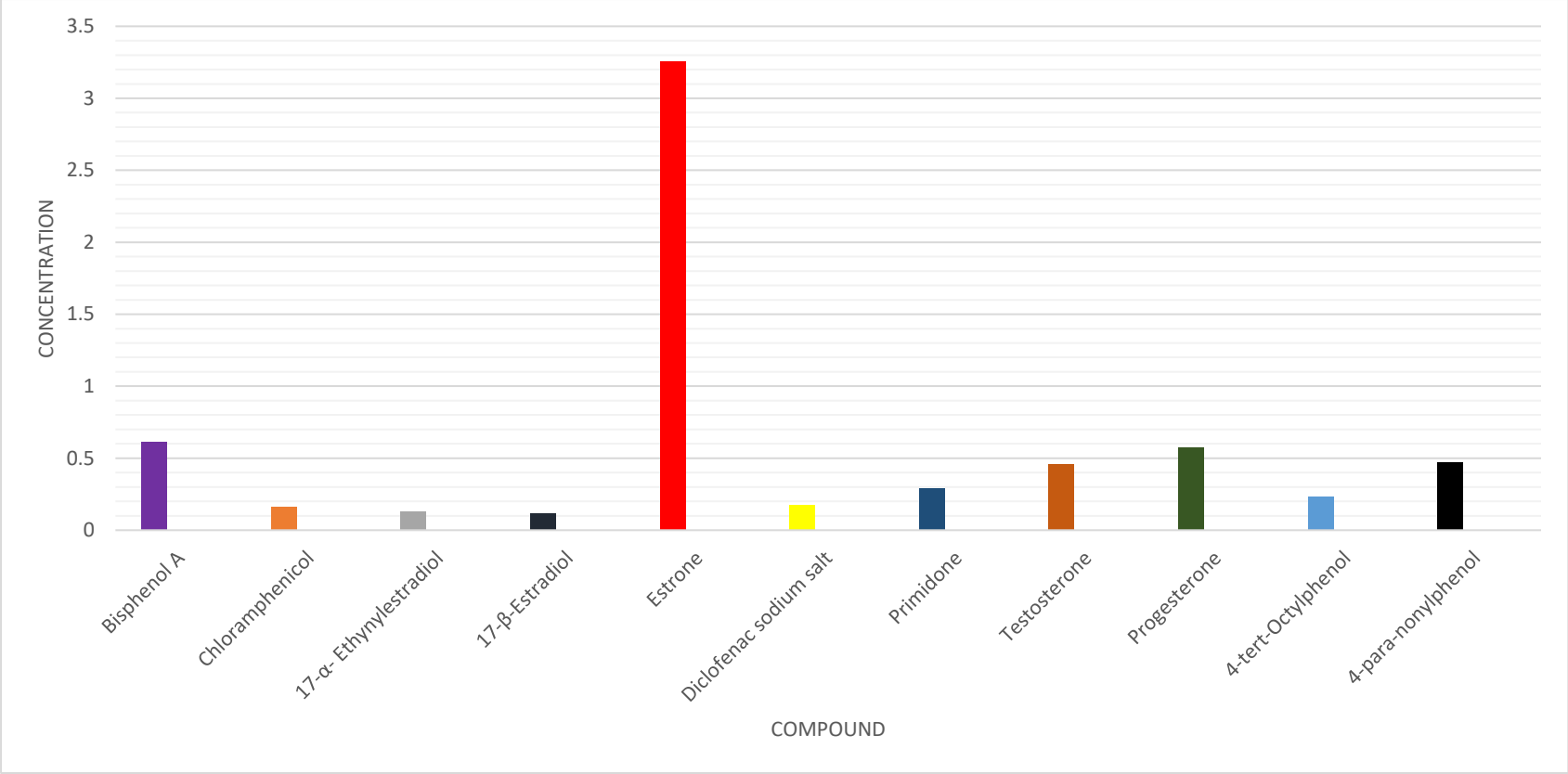


Figure 8. Mean concentration (µg/L) of analyte in raw water from DWTP dam, Takoradi.

Source: Field work (2020

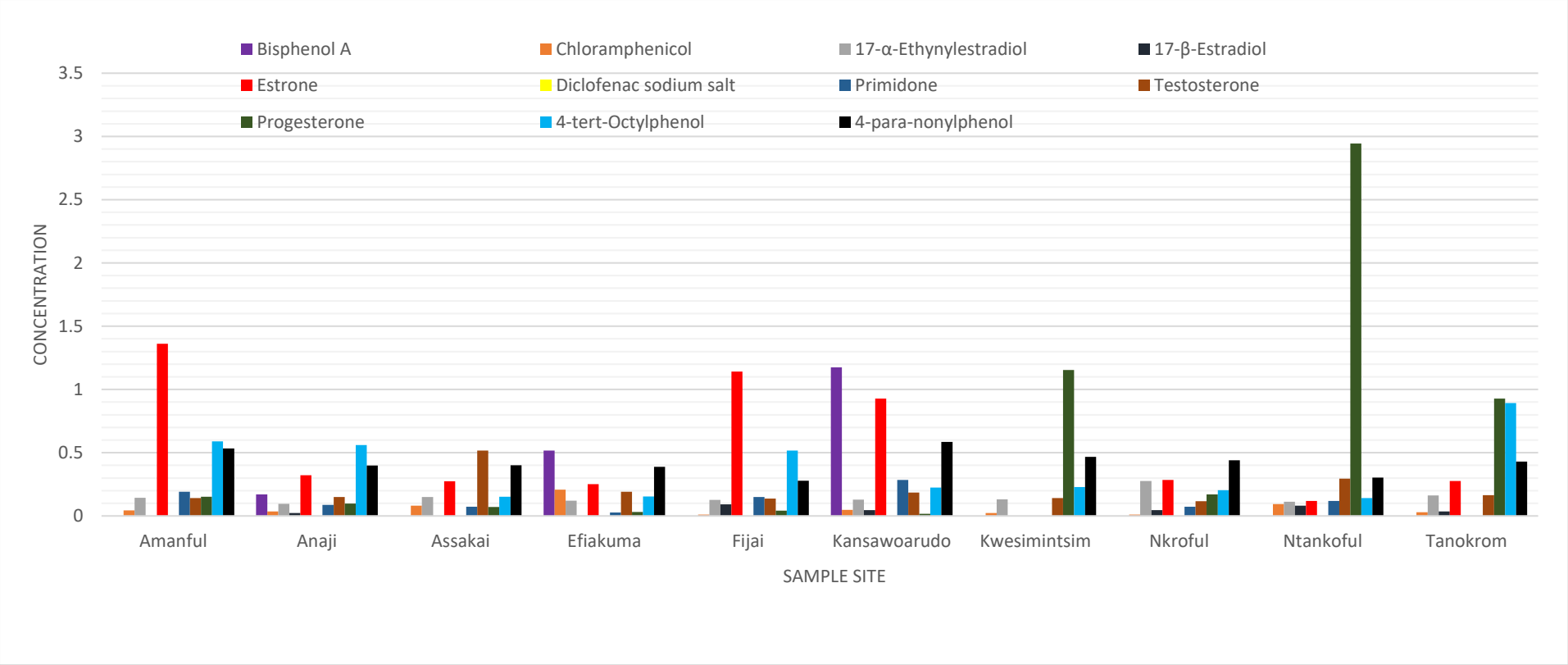


Figure 9. Mean concentration of analytes in tap water from ten (10) communities within Takoradi

Source: Field work (2020).

Overview 0f Occurrence and Distribution of the Selected Compounds in Cape Coast and Takoradi

Takoradi is more cosmopolitan than Cape Coast with higher population, medical facilities and industrial activities. It is therefore expedient to assume higher levels of pharmaceuticals in its water source, however the results obtained from the study indicated otherwise. Raw water samples from Cape Coast had higher concentration levels of Chloramphenicol, 17-alpha-Ethynylestradiol, 17-beta-Estradiol, Estrone, Diclofenac Sodium Salt, Progesterone, Testosterone, 4-tert-Octylphenol and 4-para-Nonylphenol than raw water samples from Takoradi. This may be due to the fact that Pra river which is the source of water for Daboase Water Treatment Plant (DWTP) mainly runs through forest areas thus polluted mainly by illegal mining activities, whiles Kakum river the source of water for Brimsu Water Treatment Plant (BWTP) runs through a lot of human settlements thus polluted highly by domestic waste especially, dump sites which are major sources of these compounds in water.

Apart from 17-beta-Estradiol, the average concentration of all the other ten (10) compounds analyzed in the study were higher in tap water from Cape Coast than those sampled in Takoradi, which is in agreement with reasons stated earlier on the pollution of Kakum River as well as the efficiency of the treatment method employed at BWTP in removing these compounds. It could also be due to cross contamination with the compounds during distribution thereby each sample had different levels of the detected compounds. The highest concentration of Bis-phenol A in raw water collected at the dam of DWTP was 1.207 µg/ and 0.417 µg/L in samples from the dam of BWTP. Bis-

phenol A concentration in raw water from DWTP were therefore elevated compared to the 0.42 µg/L reported by Elobeid et al., (2012). The concentration of Bis-phenol A in tap water analyzed in this study ranged from 0.171to1.174 µg/L for Takoradi and 0.172 to1.737 µg/L for Cape Coast. These levels are comparable to the 251 ng/mL (0.251 µg/L) reported by Karalius et al., (2020) in a review of Bis-phenol in Africa waters, but elevated compared to the 44.3 ng/L (0.0443 µg/L) reported by Padhye et al (2014) for drinking water in the USA. This may be due to ubiquitous use of plastics which are the major source of Bis-phenol A, improper disposal and lack of recycling in Takoradi and Cape Coast.

A study by K'oreje el al., (2013), in Kenya on Waste Water Treatment Plant (WWTP) influent reports non detection of Chloramphenicol in untreated water, however, this study reported an average concentration of 0.275 µg/L in raw water from BWTP dam, and 0.159 µg/L from DWTP dam. The average levels of estrogen derivative pharmaceuticals, 17-alpha-Ethynylestradiol and 17-Beta-Estradiol in tap water samples reported in this study ranged from 0.086 to1.325 µg/L and 0.018 to 0.064 µg/L respectively for samples collected in Cape Coast. That of Takoradi were 0.096 to 0.27 µg/L and 0.024 to 0.092 µg/L respectively. These levels are elevated compared to a study in Brazil where concentration levels were below the method LOQ of 13.9 ng/L (0.013 µg/L) for 17-alpha-Ethynylestradiol and 5.9ng/L (0.0059 µg/L) for 17-beta-Estradiol. (Solano et al., 2015). The levels of Estrone in tap water, from this study 0.268 to 12.324 µg/L for are Cape Coast and 0.119 to 1.362 µg/L for Takoradi respectively. The levels of Estrone were elevated compared to the

0.9 ng/L (0.0009 µg/L) recorded in Iran by Forghaniet al., (2018) and <10ng/L (<0.001 µg/L) reported by Benotti et al., (2008) in USA.

A study of untreated water in South Africa by Manickum and John, (2014), reports lower average concentrations of Estrone (0.023 µg/L) compared to tap water samples in this study. The elevated levels of Estrone in both raw and tap water analyzed in this study may be due to pollution of source waters and the ineffectiveness of water treatment methods employed by GWCL in removing Estrone as a contaminant. Diclofnac sodium salt concentration in tap water from Cape Coast, ranged between 0.160 and 14.625 µg/L was elevated compared to the <10 ng/L (0.00 µg/L)1 reported in a study in the USA (Benotti et al., 2008). The levels of Diclofenac sodium salt in tap water from Cape Coast was also greater than the levels in the sewage water treatment effluent reported in the United Kingdom (U.K) by World Health Organization (WHO, 2012) and drinking water in Portugal (0.001 (Jesus et al., 2012). The concentration of this non-steroidal anti-inflammatory drug in the drinking water from this study was higher compared to a study by Schröder (2010), where its levels were lower than the detection limit and 6 ng/L (0.006 µg/L) reported in Germany by Jones et al, (2005), but lower than the 3000 ng/L (3.0 µg/L) reported in effluents from treatment plants in Europe (Al-Qaim et al., 2015), as well as 5049ng/L (5.049 µg/L) in Asia (Geissen and Gal, 2008). Studies in Algeria by Kermia et al. (2016) and South Africa by Agunbiade and Moodley (2016) however reported higher levels of Diclofenac sodium salt in raw water of 2.3 and 22.3 µg/L. Meanwhile, K'oreje et al., (2016) reports a concentration range of 0.93 to 1.51µg/L in untreated water in Kenya which is comparable to raw water sampled at Cape Coast. On the other

hand, Diclofenac sodium salt levels were below detection limit in tap water from Takoradi.

Progesterone and Testosterone concentrations in tap water from Cape Coast ranged from 0.018 to1.107 µg/L and 0.145 to 0.332 µg/L respectively. Whiles levels recorded in tap water from Takoradi ranged from 0.031 to 2.944 µg/L and 0.117 to 0.516 µg/L respectively. The levels of Progesterone and Testosterone in this study were higher in both metropolis than the concentration of <10 ng/L reported in a study by Benotti et al; (2009). The concentration levels reported in the study were also above the levels in drinking water reported in Brazil (<2.7 ng/L for Progesterone and <1.7 ng/L for Testosterone) by Solano et al. (2015). Progesterone and Testosterone levels in raw water from Cape Coast ranged from 0.859 to 1.607 µg/L and 0.197 to 1.03 µg/L respectively and 0.450 to 0.661 µg/L, 0.316 to 0.734 µg/L respectively for samples from Takoradi. These levels are in agreement with the 0.408 µg/L and 0.343µg/L for Progesterone and Testosterone respectively, reported in South Africa by Manickum and John (2014).

4-para-Nonylphenol concentrations in tap water from Cape Coast ranged from 0.710 to 5.887 and 0.278 to 0.585 µg/L for Takoradi. These levels are elevated compare to the (<10.6 ng/L) reported by Solano et al., (2015) as well as occurrence in the treated ground and surface water concentration reported globally in a study by Wee and Aris, (2017).

The persistent elevated levels of most of the compounds reported in this study even after treatment compared to other studies could perhaps be as a result of lack of wastewater treatment plants and indiscriminate disposal of pharmaceuticals and other product such as plastic water bottles, baby feeding

bottles, lubricants, fungicides, detergents and personal care products which contain endocrine active chemicals. Also, the efficiency of the treatment methods used at the water treatment plants in both Cape Coast and Takoradi may be weak compared to efficiency of treatment plants in the USA as reported by Li et al. (2013).

Source Apportionment

Absolute Principal Component Analysis with multi linear regression (APCA-MLR) have been successfully employed for source apportionment in environmental studies (Adjei et al., 2019). Pharmaceuticals and endocrine active compounds are introduced into ground and surface water through; wastewater effluents from industries, hospitals, homes and wastewater treatment plants (Hartmann et al., 1999, Fick et al., 2009, Koplin et al., 2002), agricultural and veterinary usage (Hollis and Ahmed 2013), as well as landfill and sewage disposal sites (Sui et al , 2015). The APCA-MLR were conducted so likely sources could be apportioned for the pharmaceuticals in raw and tap water in Cape Coast and Takoradi. Component matrix from the PCA indicated a mixed module with four (4) significant components (KMO = 0.494) after verimax with Kaiser Normalization rotation and Eigenvalues = 1(Table 3).

The four (4) factor components contributed about 71.96% of the total percent variance. Factor component 1 (FC1) had high loading (>0.500) for Bis-phenol A, Primidone, 17-alpha-Ethynylestradiol, Testosterone and 4-tert-Octylphenol. Factor component 2 (FC2) loaded high for 17-beta-Estradiol and Chloramphenicol. Factor component 3 (FC3) had high loading for Estrone and 4 - para-Nonylphenol. Factor component 4 (FC4) loaded high for Diclofenac sodium salt. (Table 3). FC1 is suggestive of a dumpsite, due to indiscriminate

disposal of waste in the study and the diverse nature of the compounds that formed its component. Wastewater from hospitals could be likened FC2 whiles components for FC3, Estrone which is excreted naturally by humans and 4-para-Nonylphenol which is predominantly used in the manufacture of personal care product could be from domestic wastewater. Diclofenac sodium salt, the prominent component of FC4 could have been introduced into the raw water through the veterinary use of this anti-inflammatory drug especially on cattle farms. Component plot in rotated space (Fig.9), also indicated a much greater loading for one (1) of the four (4) sources which was comparable to the high loading for FC1 from the factor extraction.

Table 3: Component Matrix from the Principal Component Analysis

	Component			
	1	2	3	4
BPA	.714	-.398	-.161	.142
Chlo	.204	.644	.275	.239
17-Alpha	.648	-.622	-.095	-.174
17-beta	.554	.655	.080	-.224
Estrone	.457	.217	.768	.036
Diclo	-.163	.106	-.276	.551
Primi	.730	.173	-.396	.288
Tes	.556	.376	-.301	.365
Pro	.359	.342	.085	-.600
4-tert	.545	-.639	.200	-.064
4-para	-.005	-.289	.725	.512

BPA= Bisphenol A, Chl o= Chloramphenicol, 17-Alpha = 17-alpha-Ethynylestradiol, 17-beta =17-beta-Estradiol, Diclo= Diclofenac sodium salt, Primi= Primidone, Tes=Testosterone, Pro= Progesterone, 4-tert = 4-tert-Octylphenol, 4-para=4-para-Nonylphenol

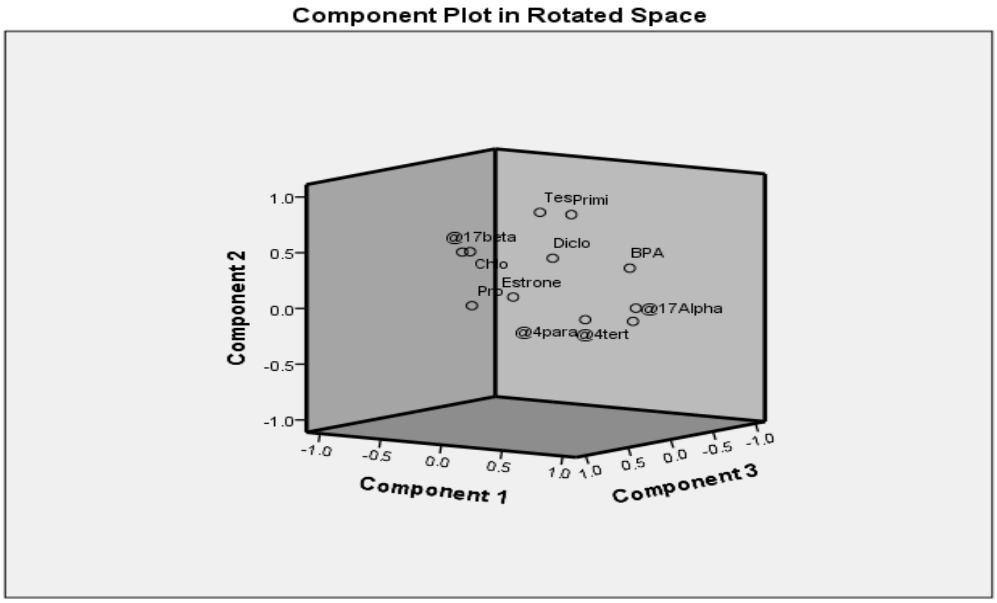


Figure 10. The PCA component plot showing the source apportionment of pharmaceuticals in raw and tap water from Cape Coast and Takoradi.

The reproduced correlation matrix (Table 4) of the factor component analysis suggested a very strong positive correlation between Bis-phenol A, 17-Alpha-Ethynylestradiol, 4-tert-Octylphenol and Primidone which are all component of FC1 thereby confirming FC1 as the common source. Chloramphenicol also showed strong positive correlation with 17-beta-Estradiol (FC2). Diclofenac sodium salt showed a moderate negative correlation with most of the analytes (Table 4). This is comparable to the factor extraction, thus Diclofenac sodium salt loading significantly for FC4 than any other compound analyzed in this study.

For the source apportionment to be complete, FCs (sources) contributions to the compounds were determined with a combined PCA-MLR analysis. The four factor components were used as the dependent variables whereas the analytes were used as the independent variables. The results

obtained showed a perfect level of prediction for the data (R=1.000, R^2 =1.000) and also the ANOVA model as the perfect fit for the data.

Table 4: Principal Component Correlation matrix of the Analytes

		BPA	Chlo	17-Alpha	17-beta	Estrone	Diclo	Primi	Tes	Pro	4-tert	4-para
Correlation	BPA	1.000	-.083	.665	.139	.126	-.058	.482	.233	-.022	.439	.055
	Chlo	-.083	1.000	-.264	.406	.295	-.062	.231	.245	.084	-.202	.069
	17-Alpha	.665	-.264	1.000	-.008	.074	-.152	.290	.075	.134	.693	.017
	17-beta	.139	.406	-.008	1.000	.513	-.030	.352	.351	.444	-.080	-.305
	Estrone	.126	.295	.074	.513	1.000	-.138	.090	.072	.233	.224	.446
	Diclo	-.058	-.062	-.152	-.030	-.138	1.000	.043	.102	-.134	-.179	.042
	Primi	.482	.231	.290	.352	.090	.043	1.000	.623	.075	.214	-.199
	Tes	.233	.245	.075	.351	.072	.102	.623	1.000	.181	-.011	-.037
	Pro	-.022	.084	.134	.444	.233	-.134	.075	.181	1.000	.037	-.190
	4-tert	.439	-.202	.693	-.080	.224	-.179	.214	-.011	.037	1.000	.243
	4-para	.055	.069	.017	-.305	.446	.042	-.199	-.037	-.190	.243	1.000

Source; Field work, 2020.

Chapter Summary

The results obtained from the quality control measures as well from the analyses of the water samples are presented in this chapter. Statistical presentations of these results are also outlined in this chapter. Finally, this chapter discussed results from this study in comparison with similar studies from different parts of the world.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Summary

Raw and tap water collected across Cape Coast and Takoradi metropolises were taken through SPE followed by HPLC analysis. The concentrations obtained were elevated than reported levels of same analytes in raw and tap water from Europe, USA as well as Brazil but comparable with levels reported in studies from other parts of Africa countries.

All eleven (11) selected compounds were determined and quantified in the raw water from Cape Coast (BWTP dam) and Takoradi (DWTP dam). Levels obtained ranged from 0.185 to 21.011 µg/L and 0.028 to 3.642 µg/L respectively, with Estrone levels being the highest at both locations.

Bis-phenol A, Estrone, Testosterone, 4-tert-Octylphenol and 4-para-Nonylphenol were identified and quantified above method LOD in tap water samples collected from ten (10) communities across Cape Coast, at levels ranging from 0.018-14.625 µg/L and Estrone recording the highest concentration. On the other hand, Chloramphenicol, 17-alpha-Ethynlestradiol, Testosterone, Progesterone, 4-tert-Octylphenol and 4-para-Nonylphenol were determined in all the ten (10) samples of tap water collected in ten (10) different communities across Takoradi. Levels recorded ranged from 0.011 to 2.944 µg/L. Diclofenac sodium salt was however not detected in any of the tap water sample from Takoradi, this, may be due to the efficiency of the water treatment processes employed by GWCL at DWTP in removing Diclofenac sodium salt.

Even though the levels of these compounds in tap water samples analyzed in this study were elevated compared to levels reported by studies in the western world, they were lesser than levels recorded by the raw water samples analyzed in this study. This suggested some degree of removal of these compounds after conventional water treatment processes applied by GWCL at BWTP and DWTP. However, the differences in concentration levels of a particular analyte in the twenty (20) individual tap water samples from both cities indicated a possible cross contamination of tap water during distribution to the various communities.

APCA-MLR conducted revealed four (4) factor components (FC's) as major sources responsible for the presence of the compounds in the source waters. These four (4) were apportioned to dumpsite (FC1) indiscriminate disposal of waste in the study area, wastewater from medical facilities (FC2), domestic wastewater (FC3) and veterinary usage (FC4). FC1 had high loading for Bis-phenol A, 17-alpha-Ethynylestradiol, 17-beta-Estradiol, Primidone, Testosterone and 4-tert-Octylphenol. Chloramphenicol and 17-beta-Estradiol loaded high for FC2, Estrone and 4-para-Nonylphenol for FC3 while Diclofenac sodium salt loaded highly for FC4.

Conclusions

The analysis of the sampled raw and tap water showed elevated levels of the eleven (11) selected pharmaceuticals and endocrine disrupting compounds. A comparison of levels of the compounds in raw water to tap water indicated a degree of removal after conventional water treatment. APC-MLR of the results implied the compounds were introduced into the analyzed waters through four (4) signature sources.

Recommendations

Concerns have been raised over the existence of pharmaceuticals and endocrine active compounds in tap/drinking water, but exposure of these compounds in tap water is unavoidable and expected for relatively long periods. Therefore, in view of the results and the conclusions obtained, this study purports to recommend the following;

1. Alternative or advanced drinking-water treatment to eliminate or minimize the amounts of pharmaceuticals and endocrine disrupting compounds in drinking-water are required.
2. Routine screening systems for pharmaceuticals and endocrine disrupting compounds in drinking water should be considered in the treatment processes.
3. There should be further studies and discussions into the effects of long term exposure to low levels of these in drinking water to protect public health.
4. Treatment of wastewater in major cities to reduce the pollution of source of drinking water treatment plants.
5. This study should be replicated in other parts of the country to get realistic data which will help in decision making by stake holders.

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APPENDICES

APPENDIX A

TABLE A1: CALIBRATION CURVES PARAMETERS FOR THE EXTERNAL STANDARDS USED

standard	R2	R	RF%RSD
Bis-phenol A	0.9996348	0.9998174	7.414849
Chloramphenicol	0.9986477	0.9993236	6.818794
17-alpha-Ethynylestradiol	0.9989285	0.9994641	15.871622
17-beta-Estradiol	0.9994286	0.9997142	52.877260
Estrone	0.9991855	0.999592	26.210118
Diclofenac sodium salt	0.9996314	0.9998157	11.151790
Primidone	0.9991634	0.9995816	3.389046
Testosterone	0.9997327	0.9998663	8.021877
Progesterone	0.9986796	0.9993396	10.584965
4-tert-Octylphenol	0.9958238	0.9979097	12.439570
4-para-nonylphenol	0.9996947	0.9998473	16.753430

Source: Field work 2020

CONTINUATION OF APPENDIX A

TABLE A2: MEAN CONCENTRATION (µg/L) OF THE SELECTED COMPOUNDS (n=3) IN RAW WATER FROM BWTP DAM

Analyte	Dam Site 1	Dam Site 2	Dam Site 3	Mean of mean
Bis-Phenol A	0.417 ± 0.321	<LOD	<LOD	0.616
Chloramphenicol	0.219 ± 0.101	0.504 ± 0.000	0.345 ± 0.009	0.159
17-Alpha-Ethynylestradiol	0.185 ± 0.003	0.101 ± 0.003	<LOD	0.129
17-Beta-Estradiol	0.218 ± 0.095	0.195 ± 0.014	0.358 ± 0.000	0.115
Estrone	3.043 ± 0.620	0.448 ± 0.009	21.011 ± 0.368	3.259
Diclofenac Sodium Salt	3.392 ± 0.013	1.340 ± 0.017	0.197 ± 0.004	0.175
Primidone	0.321 ± 0.003	0.223 ± 0.011	0.190 ± 0.013	0.290
Testosterone	1.034 ± 0.001	0.264 ± 0.006	0.197 ± 0.004	0.460
Progesterone	0.859 ± 0.025	<LOD	1.607 ± 1.026	0.572
4-tert-Octylphenol	0.578 ± 0.242	0.303 ± 0.006	0.412 ± 0.137	0.233
4-Para-Nonylphenol	1.244 ± 0.037	2.218 ± 0.254	0.474 ± 0.007	0.473

Source: Field Work (2020)

CONTINUATION OF APPENDIX A

TABLE A3: MEAN CONCENTRATION (µg/L) OF THE SELECTED COMPOUNDS (n=3) IN TAP WATER FROM TEN (10) COMMUNITIES WITHIN CAPE COAST.

Pharmaceutical	Abura	Amisano	Brabedze	Brafoyaw	CP Bus Stop	Mempeasem	Ola	Pedu Village	4th Ridge	Royal Lane Abease
Bis-Phenol A	0.217 ± 0.001	1.737 ± 0.000	0.172 ± 0.013	0.195 ± 0.057	0.476 ± 0.007	0.240 ± 0.020	0.217 ± 0.001	0.238 ± 0.013	0.239 ± 0.006	0.213 ± 0.008
Chloramphenicol	0.100 ± 0.004	<LOD	<LOD	<LOD	0.032 ± 0.000	<LOD	0.100 ± 0.004	0.201 ± 0.001	0.081 ± 0.001	0.073 ± 0.000
17-Alpha-Ethynylestradiol	<LOD	1.325 ± 0.599	<LOD	0.320 ± 0.001	0.232 ± 0.001	0.137 ± 0.007	0.091 ± 0.001	0.086 ± 0.002	0.150 ± 0.005	0.126 ± 0.000
17-Beta-Estradiol	<LOD	0.069 ± 0.062	0.030 ± 0.000	<LOD	0.020 ± 0.004	0.018 ± 0.008	<LOD	<LOD	<LOD	<LOD
Estrone	7.992 ± 0.107	8.764 ± 0.000	0.305 ± 0.004	1.278 ± 0.386	2.016 ± 0.518	11.089 ± 0.500	7.992 ± 0.107	12.324 ± 0.092	1.482 ± 0.100	0.268 ± 0.003
Diclofenac Sodium Salt	<LOD	<LOD	14.625 ± 0.296	<LOD	<LOD	<LOD	<LOD	<LOD	0.160 ± 0.011	<LOD
Primidone	<LOD	0.318 ± 0.000	0.121 ± 0.000	0.074 ± 0.005	0.132 ± 0.003	0.091 ± 0.007	0.099 ± 0.001	0.097 ± 0.002	0.283 ± 0.011	0.094 ± 0.000
Testosterone	0.262 ± 0.000	0.326 ± 0.100	0.187 ± 0.001	0.194 ± 0.000	0.332 ± 0.002	0.292 ± 0.004	0.262 ± 0.000	0.214 ± 0.001	0.247 ± 0.001	0.145 ± 0.001
Progesterone	<LOD	1.107 ± 0.000	<LOD	0.062 ± 0.000	0.117 ± 0.062	0.358 ± 0.008	0.340± 0.000	0.541 ± 0.005	0.419 ± 0.085	0.018 ± 0.001
4-tert-Octylphenol	0.250 ± 0.007	2.324 ± 0.650	0.114 ± 0.005	1.118 ± 0.086	0.591 ± 0.004	0.792 ± 0.008	0.250 ± 0.007	1.192 ± 0.001	1.836 ± 0.095	0.738 ± 0.003
4-Para-Nonylphenol	5.887 ± 0.004	2.925 ± 0.000	2.254 ± 0.009	1.245 ± 0.059	0.710 ± 0.023	3.160 ± 0.124	5.887 ± 0.004	7.131 ± 0.024	1.397 ± 0.015	4.263 ± 0.031

Source: Field Work 2020

CONTINUATION OF APPENDIX A

TABLE A4: MEAN CONCENTRATION (µg/L) OF THE SELECTED COMPOUNDS (n=3) IN RAW WATER FROM DWTP DAM

Analyte	Dam Site 1	Dam Site 2	Dam Site 3	Mean of mean
Bis-Phenol A	1.207 ± 1.221	0.283 ± 0.137	0.359 ± 0.042	0.616
Chloramphenicol	0.244 ± 0.030	0.117 ± 0.015	0.117 ± 0.016	0.159
17-Alpha-Ethynylestradiol	0.125 ± 0.000	0.159 ± 0.001	0.104 ± 0.000	0.129
17-Beta-Estradiol	0.159 ± 0.078	0.157 ± 0.099	0.028 ± 0.004	0.115
Estrone	3.212 ± 0.040	3.642 ± 0.004	2.922 ± 0.079	3.259
Diclofenac Sodium Salt	0.074 ± 0.082	0.234 ± 0.00	0.218 ± 0.047	0.175
Primidone	0.183 ± 0.004	0.258 ± 0.230	0.430 ± 0.004	0.290
Testosterone	0.329 ± 0.001	0.316 ± 0.000	0.734 ± 0.001	0.460
Progesterone	0.450 ± 0.613	0.661 ± 0.649	0.605 ± 0.019	0.572
4-tert-Octylphenol	0.429 ± 0.005	0.156 ± 0.005	0.113 ± 0.001	0.233
4-Para-Nonylphenol	0.312 ± 0.005	0.720 ± 0.016	0.388 ± 0.000	0.473

Source: Field work 2020

CONTINUATION OF APPENDIX A

TABLE A5: MEAN CONCENTRATION (µg/L) OF THE SELECTED COMPOUNDS (n=3) IN TAP WATER FROM TEN (10) COMMUNITIES WITHIN TAKORADI

Analyte	Amanful	Anaji	Assakai	Effiakuma	Fijai	Kansokorado	Kwesimintsim	Nkroful	Ntankoful	Tanokrom
Bis-Phenol A	<LOD	0.171 ± 0.000	<LOD	0.516 ± 0.002	<LOD	1.174 ± 0.053	<LOD	<LOD	<LOD	<LOD
Chloramphenicol	0.043 ± 0.000	0.036 ± 0.005	0.081 ± 0.031	0.207 ± 0.206	0.011 ± 0.004	0.049 ± 0.064	0.023 ± 0.018	0.011 ± 0.001	0.093 ± 0.006	0.030 ± 0.000
17-Alpha-Ethynylestradiol	0.143 ± 0.001	0.096 ± 0.000	0.146 ± 0.071	0.121 ± 0.003	0.126 ± 0.001	0.130 ± 0.001	0.132 ± 0.000	0.270 ± 0.121	0.113 ± 0.000	0.162 ± 0.002
17-Beta-Estradiol	<LOD	0.024 ± 0.009	<LOD	<LOD	0.092 ± 0.087	0.045 ± 0.004	<LOD	0.045 ± 0.039	0.082 ± 0.000	0.035 ± 0.017
Estrone	1.362 ± 0.023	0.322 ± 0.001	0.274 ± 0.000	0.252 ± 0.006	1.142 ± 0.029	0.928 ± 0.006	<LOD	0.285 ± 0.049	0.119 ± 0.154	0.277 ± 0.001
Diclofenac Sodium Salt	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Primidone	0.192 ± 0.023	0.087 ± 0.018	0.074 ± 0.000	0.028 ± 0.003	0.149 ± 0.045	0.285 ± 0.011	<LOD	0.073 ± 0.001	0.119 ± 0.000	<LOD
Testosterone	0.141 ± 0.000	0.149 ± 0.001	0.516 ± 0.000	0.192 ± 0.000	0.138 ± 0.002	0.186 ± 0.001	0.141 ± 0.001	0.117 ± 0.001	0.294 ± 0.115	0.164 ± 0.000
Progesterone	0.151 ± 0.094	0.098 ± 0.081	0.070 ± 0.003	0.031 ± 0.013	0.042 ± 0.004	0.016 ± 0.005	1.153 ± 0.013	0.171 ± 0.013	2.944 ± 0.011	0.928 ± 0.002
4-tert-Octylphenol	0.590 ± 0.006	0.561 ± 0.001	0.151 ± 0.004	0.154 ± 0.004	0.517 ± 0.003	0.225 ± 0.002	0.228 ± 0.001	0.204 ± 0.008	0.141 ± 0.005	0.892 ± 0.013
4-Para-Nonylphenol	0.534 ± 0.013	0.399 ± 0.021	0.400 ± 0.003	0.389 ± 0.005	0.278 ± 0.001	0.585 ± 0.008	0.467 ± 0.009	0.441 ± 0.226	0.304 ± 0.000	0.429 ± 0.018

Source: Field work 2020

CONTINUATION OF APPENDIX A

TABLE A6: TOTAL VARIANCE FROM THE PRINCIPAL COMPONENT ANALYSIS

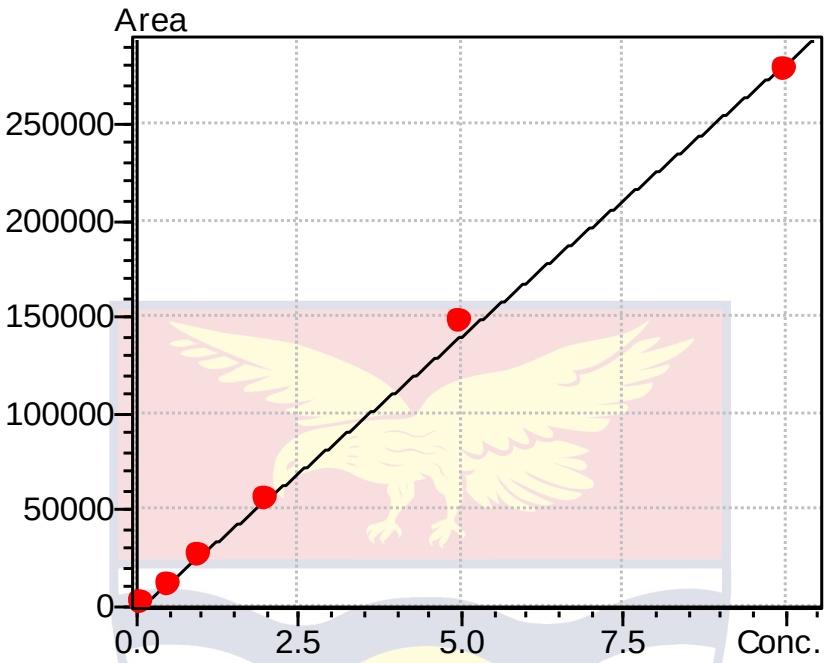
	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.781	25.278	25.278	2.781	25.278	25.278	2.441	22.191	22.191
2	2.227	20.246	45.524	2.227	20.246	45.524	2.169	19.721	41.912
3	1.603	14.574	60.097	1.603	14.574	60.097	1.688	15.344	57.256
4	1.305	11.867	71.964	1.305	11.867	71.964	1.618	14.708	71.964
5	.896	8.145	80.109						
6	.675	6.137	86.246						
7	.501	4.550	90.796						
8	.443	4.026	94.822						
9	.280	2.548	97.370						
10	.187	1.704	99.075						
11	.102	.925	100.000						

Source: Field work 2020

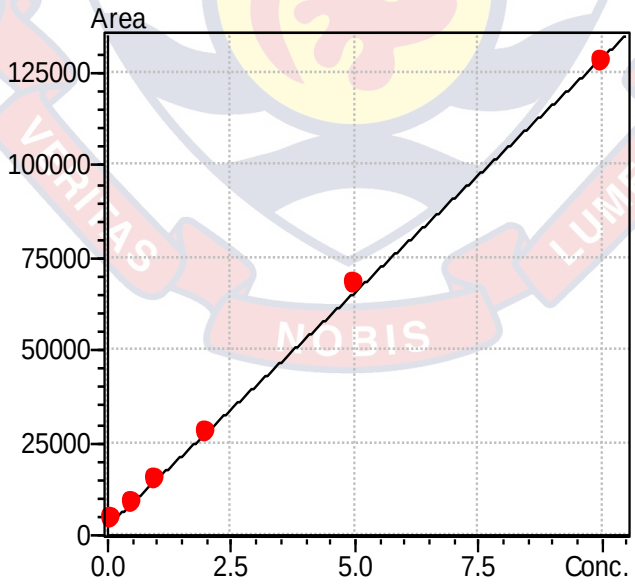
APPENDIX B

CALIBRATION CURVES FOR THE EXTERNAL STANDARDS USED

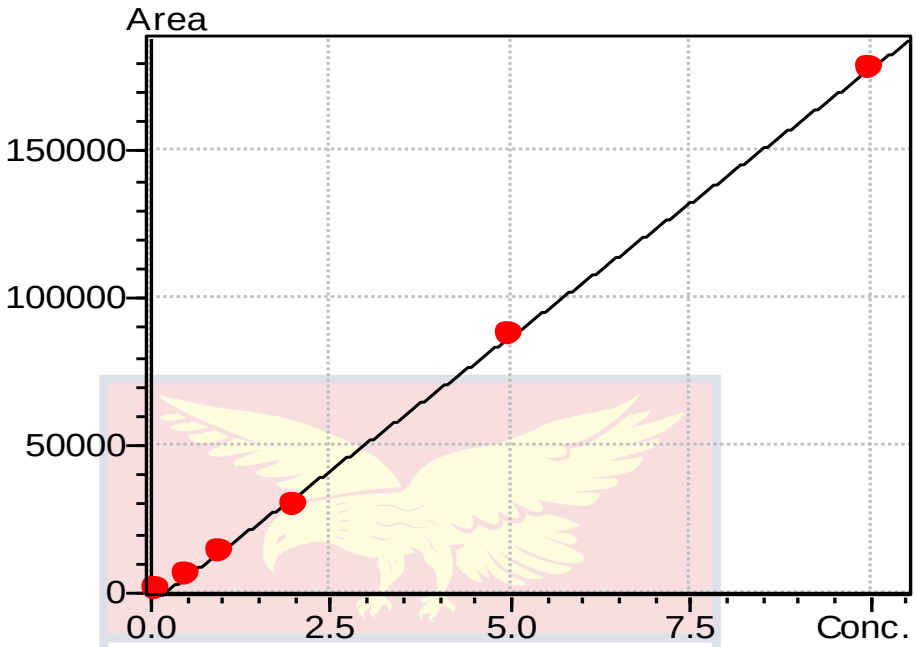
1.17-ALPHA-ETHYNYLESTRADIOL



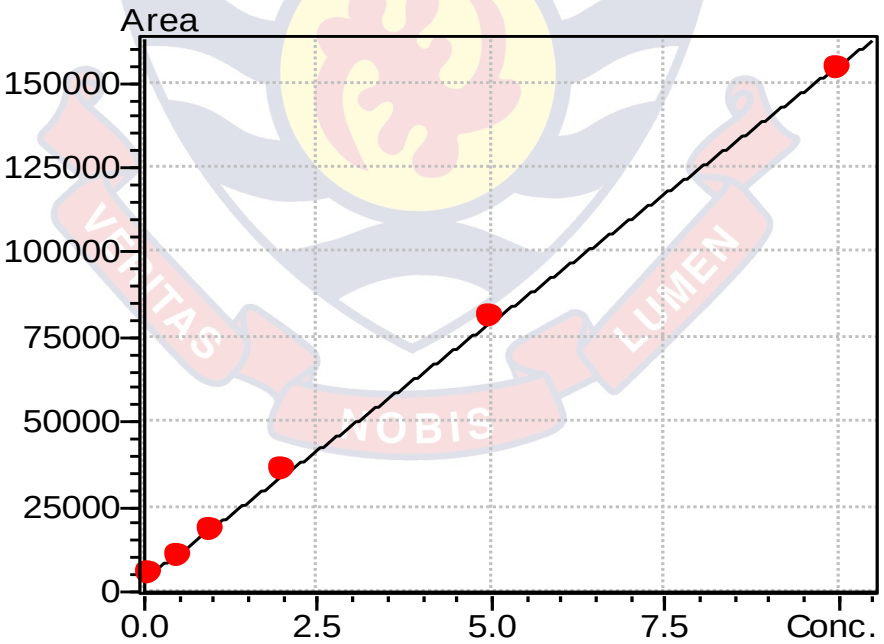
2. 17-BETA-ESTRADIOL



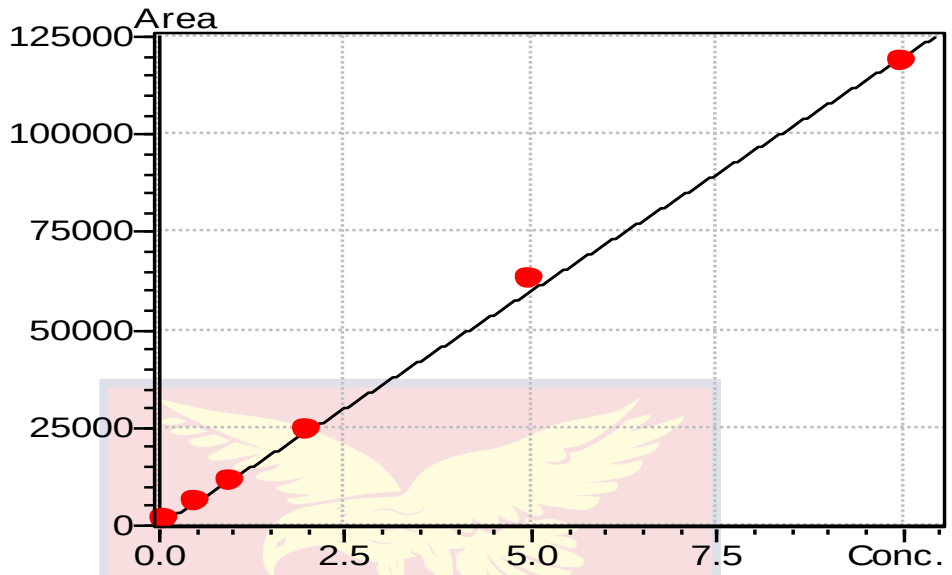
3. ESTRONE



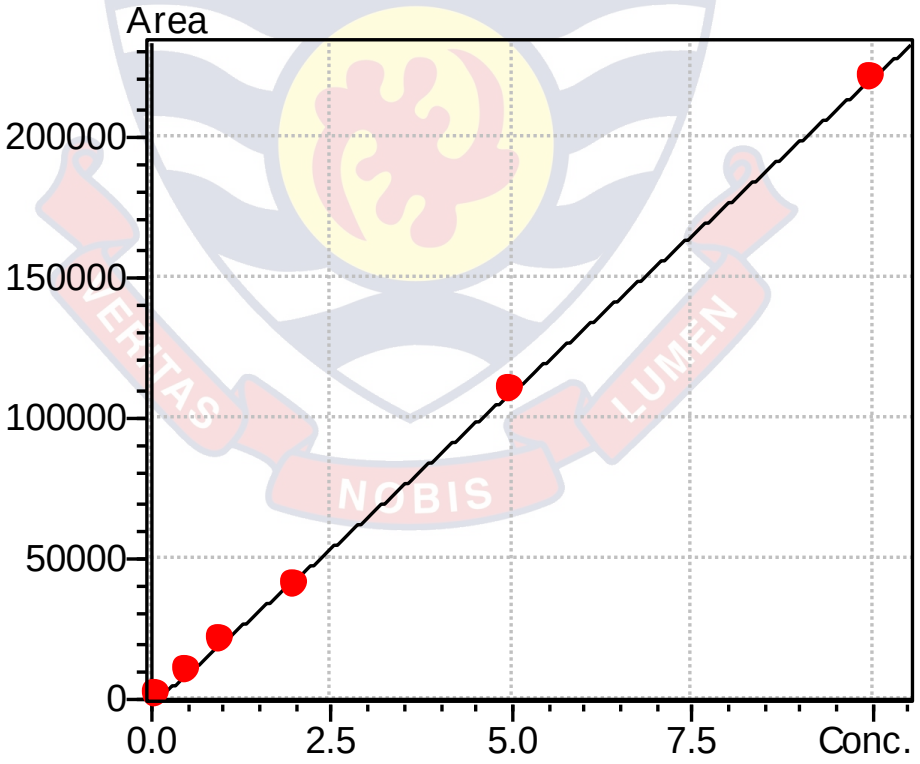
4. DICLOFENAC SODIUM SALT



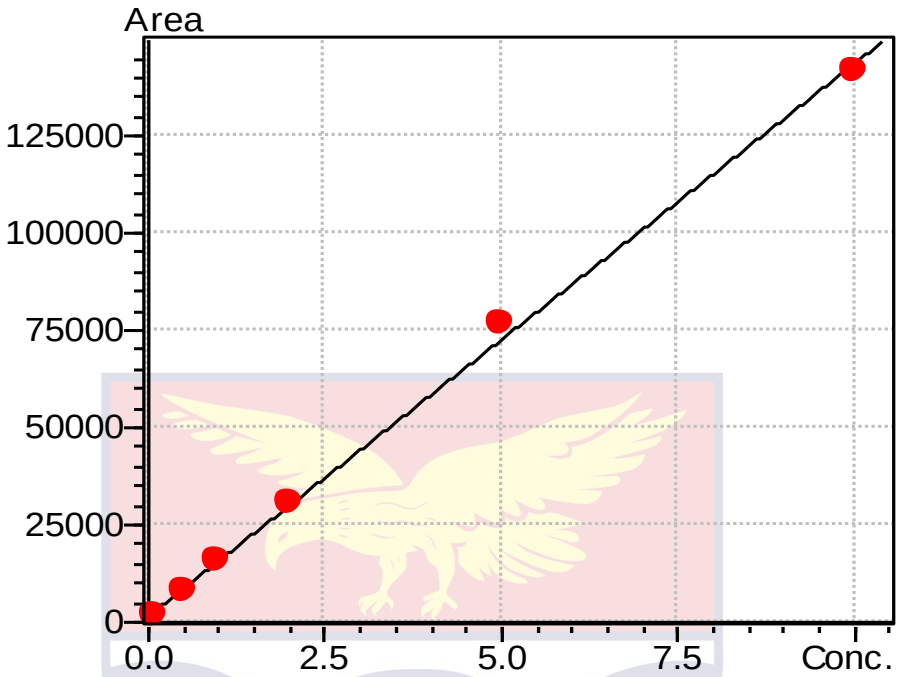
5. PRIMIDONE



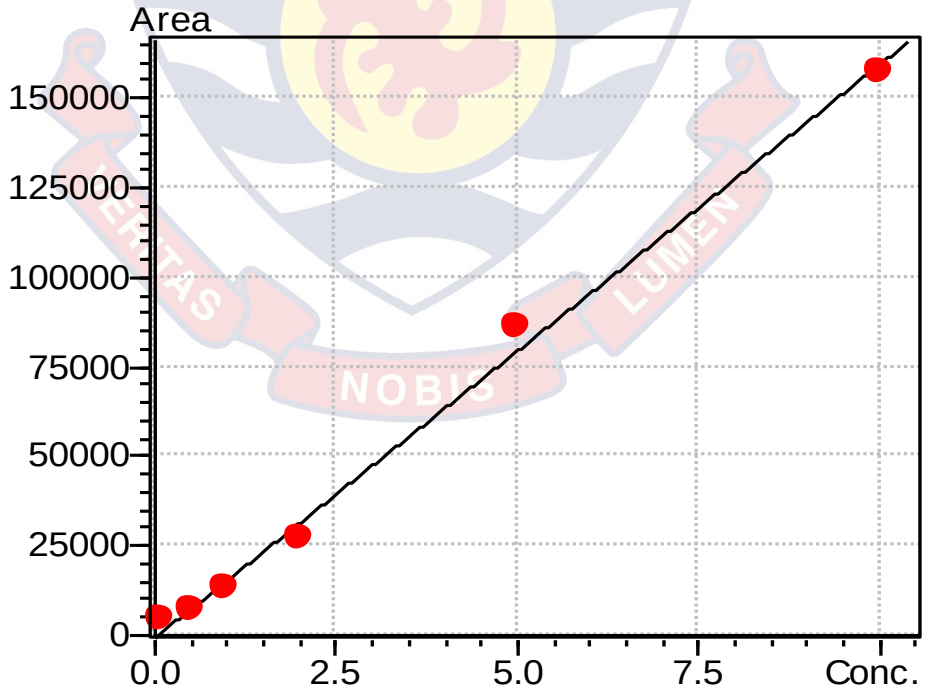
6. TESTOSTERONE



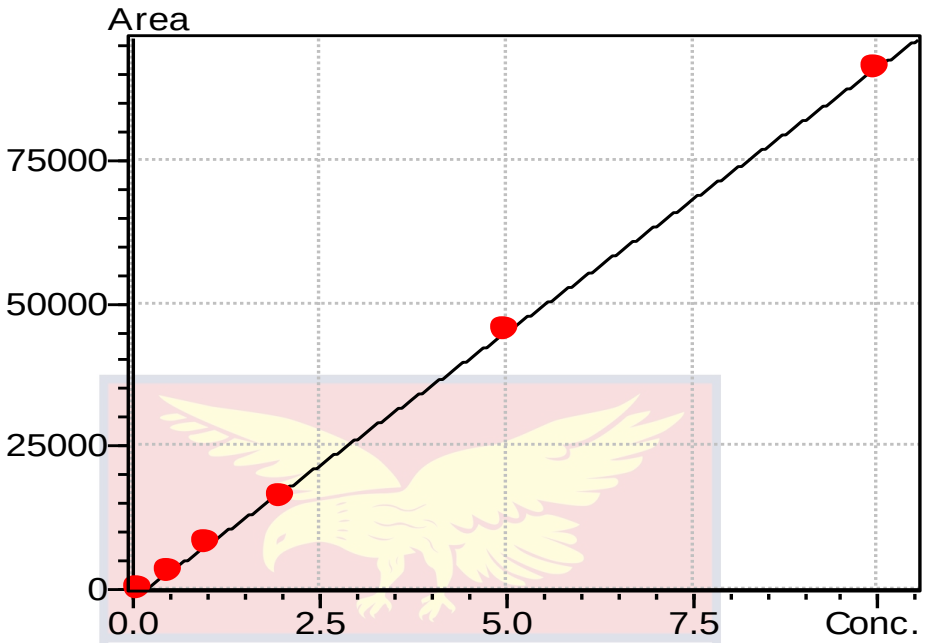
7. PROGESTERONE



8. 4-TERT-OCTYLPHENOL

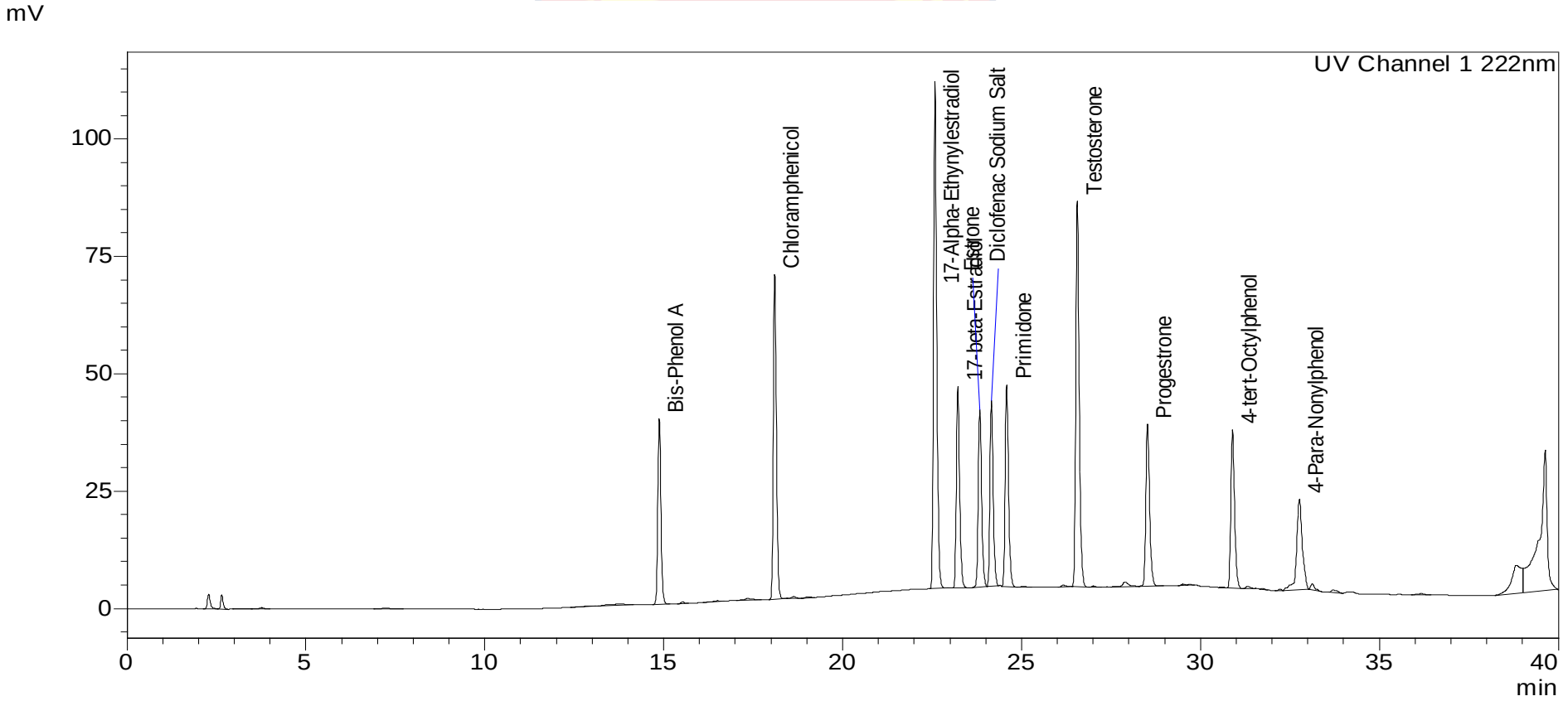


9. 4-PARA-NONYLPHENOL



APPENDIX C

CHROMATOGRAPH OF THE EXTERNAL STANDARDS USED



VERITAS
NOBIS
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