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Investigation of Some Pharmaceutically Active Compounds (PHACS) in Soil and Sediment Around Selected Drug Manufacturing Companies in Lagos

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Abstract: *The problem of pharmaceutically active compounds (PhACs) in environment has been at forefront of current researches by environmental scientists. Pharmaceuticals, when present in environmental media could induce resistance in micro-organisms which could eventually result in hazard to human. Due to the growing cause of drug resistance by many microorganisms the aim of this study was to investigate PhACs in soil and sediment around the catchments of selected pharmaceutical manufacturing company in Lagos Nigeria. Soil and sediment samples were collected from different locations (Ologe Lagoon Sediment (OLS), Agbara Residential Area soil (ARS), Isolo Canal Sediment (ICS), Isolo Borehole area soil (IBS)). The selected PhACs were extracted from soil and sediment using ultrasound assisted extraction (UAE) and subsequently concentrated and cleaned up using solid phase extraction (SPE). After air-drying and re-dissolution of extract in 1 ml of methanol, the extract was analysed using HPLC with UV detector for quantification of the PhACs (Amoxicillin, Pyrimethamine, Sulfadoxine). The results obtained showed that Ologe lagoon sediment had the highest average sulfadoxine concentration of 1.13 µg/g. The average concentrations of pyrimethamine were 0.107 µg/g, 0.0243 µg/g, 0.090 µg/g, and 0.023 µg/g OLS, ARS, ICS and IBS respectively with OLS having the highest average concentration which positively correlate to sulfadoxine concentration in same River. Amoxicillin was not detected in all the samples, thus its concentration were probably below detection limit of the UV detector applied. Total organic carbon (TOC %) correlation coefficients were N/A, -0.2366, -06964 for amoxicillin, pyrimethamine and sulfadoxine respectively which indicate that PhACs concentration were probably not affected by TOC in the soil. The antimalarial drugs, pyrimethamine and sulfadoxine, were detected in all sampling sites except Isolo canal sediment, presence of these PhACs even at these comparatively low concentrations could lead to increased resistance to these drugs by malaria causing parasite. Considering the prevalence of malaria and other microbial infections in Nigeria, this may result in higher death rates than at present. More researches are needed for the detection and quantification of amoxicillin and other pharmaceuticals in order to generate a baseline data for this possibility.*

Keywords: pharmaceutically active compounds (PHACS), soil, sediment, drug manufacturing companies, Lagos

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INTRODUCTION

The awareness of the problem of pharmaceutically active compounds (PhACs) in the environment is increasing among scientific researchers, governments, pharmaceutical companies, and the society at large. Beginning from the mid-1990s, researchers in the field of environmental sciences have regularly explored the existence of pharmaceutically prepared drugs and their metabolites, referred to collectively as Pharmaceutically Active Compounds, in surface water groundwater river sediments soil and occasionally in drinking water (Doerr-MacEwen, 2007). These PhACs, which cause land and water pollution, are mainly human end-use pharmaceuticals (Hirsch *et al*., 1999), nevertheless veterinary pharmaceuticals from agricultural sources have also been detected in environmental samples.

The human end-use PhACs have been found in water and sediment such as samples from ocean floor and soil of wealthy nations where citizens consume relatively large quantities of pharmaceuticals, and especially in urban areas where dilution is very small. The presence of PhACs in natural waters represents a potential concern for ecosystems (Ferrari *et al*., 2003) and human hearth (Daughton and Ternes, 1999), nevertheless many scientists still believe that the adverse effect of PhACs in environment on human health is very minimal (Schulman *et al*., 2002). However, it was discovered that long term exposure to pharmaceutically active compounds in smaller doses can cause increase in resistance of microorganisms to antibiotics (Ferrari *et al*., 2003). It is pertinent to state that, notwithstanding these assertions, long term contamination of the environment by PhACS could causes detrimental effect on human lives (Kummerer *et al*., 2003). While abundant studies indicate the presence of pharmaceuticals in natural waters, very little is known about the impacts of these pharmaceuticals on aquatic ecosystems at lower doses over long period of time (Doerr-MacEwen, 2007).

Pharmaceuticals found in sediment, rivers and streams occur at extremely low concentrations usually at ultra-trace level and therefore are not expected to induce profound acute effects such as fish kills which can easily be noticed (Trudeau *et al.*, 2004). Rather, any impacts of pharmaceuticals on aquatic species and microorganisms in the soil /sediment or ecosystems are expected to be subtle, long-term, and therefore difficult to detect (Daughton and Ternes, 1999). Possibly the well-known example to date of the effects of pharmaceuticals on aquatic organisms is the feminization of male fish in rivers in the United Kingdom, due to the male fish exposure to low level synthetic hormone, 17α ethinyestradiol used as contraceptive-birth control (Jobling *et al*., 1998). While the relationships between pharmaceutically active pollutants of environment and effects on human lives in the field of environmental science researches remain so limited, nevertheless, the scientific uncertainty of the environmental risk posed by pharmaceuticals in natural waters remains high because of mixture effect of many pharmaceuticals existig together in rivers and other body of water (Brian *et al*., 2004). Many studies have demonstrated the uptake and translocation of a variety of pharmaceuticals through the root of plant with a particular focus on the antidepressant drug such as fluoxetine and antibacterial PhACs including sulfamethazine, sulfamethoxazole, trimethoprim and amoxicillin into numerous plant species

including the root and shoot of crops such as soybean, lettuce, and carrot (Lange and Dietrich, 2002).

As plants are major components of food chain for most animals and human being, in particular, the translocation of pharmaceutical drugs from soil to different plants parts could be another interface of exposure to these emerging Pollutants-PhACs in our environment.

While more scientific research into the problem of pharmaceuticals in the environment is clearly noticed in Europe, North and South America, Asia, the presence of pharmaceutically active compounds as contaminants in the Nigerian environment matrixes i.e water and soil has not been well studied. According to European Union rules and regulations concerning pollution, the precautionary principle stipulates that when a substance poses a serious threat to the environment, a lack of scientific certainty concerning the impacts should not be permitted to delay management action (Lishman *et al.*, 2006).

Pharmaceutically Active Contaminants as Emerging Pollutants in Soil and Sediments.
At the beginning of the last century, the emphasis of living organisms' exposure to PhACs in environment was on the so-called 'priority pollutants', also called Persistent organic pollutants (POPs), such as pesticides like chlorinated aromatic compounds and industrial intermediates. As environmental concerns grew and research progressed, as well as the growth in the technologies employed in detection and quantifications of organic compounds at ultra-trace level such as GC/MS, LC tandem Mass spectrometer, hand-held UV and IR instruments etc, resulting in the development of more advanced techniques and discoveries of a new group of emerging contaminants, collectively referred to as 'chemicals of emerging concern (CECs)' became more frequent (Kinney *et al*., 2006). According to Gros *et al* (2012) these chemicals of emerging concern (CECs) include pharmaceuticals (PhACs) and personal care products (PPCPs), the endocrine disrupting compounds (EDCs), per fluorinated compounds (PFCs), surfactants, fossil fuel additives, disinfection by-products, algal and cyanobacteria toxins, organometallic compounds, brominated and organophosphate flame retardants, plasticizers and nanoparticles. For the purpose of this study, the chemicals of emerging concerns (CECs) are the PHACs could be found in waste water, river, soil and the sediment of aerated ponds which could pose a serious environmental risk to living organisms after long term exposure.

According to Golon (2019), many pharmaceuticals are now regarded as chemicals of emerging concerns. These chemicals of emerging concern which must be regulated as depicted in Table 1.1, include the common antimalarial drug, chloroquine, which has buttressed the need for more study on PhACs in environment.

Table 1.1 OSPAR lists of pharmaceuticals of possible concern to the marine environment (McEneff *et al*., 2015.).

Pharmaceuticals	**Type**	**CAS Number**
Chloroquine	Antimalarial	54-05-7
Chloroquine	diphosphate Antimalarial	50-63-5
Chlorpromazine	Antipsychotic	50-53-3
Mitotane	Antineoplastic	53-19-0
Prochlorperazine	Antipsychotic/Antiemetic	58-38-8
Fluphenazine	Antipsychotic	69-23-8
Fluphenazine	dihydrochloride Antipsychotic	146-56-5
Trifluoperazine	dihydrochloride Antipsychotic	440-17-5
Trifluperidol	Antipsychotic	749-13-3
Prochlorperazine edisylate	Antipsychotic/Antiemetic	1257-78-9
Pimozide	Antipsychotic	2062-78-4
Dimetacrine tartrate	Antidepressant	3759-07-7
Niflumic acid	Anti-inflammatory	4394-00-7
Dimetacrine	Antidepressant	4757-55-5
Niclofolan	Anthelmintic	10331-57-4
Miconazole	Nitrate Antifungal	22832-87-7
Timiperone	Antipsychotic	57648-21-2
Midazolam	Anxiolitic	59467-70-8
Diammonium N-ethylheptadecafluoro-N-[2- (phosphonatooxy)ethyl] octanesulfonamidate	Chemical Auxiliary Agent	67969-69-1
Penfluridol	Antipsychotic	26864-56-2
Terofenamate	Anti-inflammatory	29098-15-5
Flunarizine	Antihypertensive	52468-60-7

OSPAR =Oslo-Paris convention, which is convention for the protection of the marine environment.

From the Table 1.1, pharmaceuticals can be classified into numerous therapeutic classes, including antinflammatories, antibiotics, antipsychotics, antihypertensives, antidiabetics, antihistamines, lipid regulators, anticonvulsant, β-blockers, stimulants and statins.
The amount of pharmaceutical productions, consumption and ultimately, discharge into the aquatic environment is steadily increasing (McEneff *et al*., 2015). Thus PhACs could be steadily introduced into Nigerian marine environment. In Nigeria, NAFDAC has licensed > 6,000 medicines for human use and > 1,000 for veterinary use (TOA Correspondent, 2020). Nigeria is

a leading potential for the pharmaceutical industry in Africa because of its enormous human population. The Nigeria market for pharmaceutical products in 2015 was pegged to reach $789 million by 2018 and artemisinin combination therapy (ACT) is most common therapy for malaria which accounts for 60% of all outpatient attendance and malaria infection is the most prevalence infection/disease in tropics (Nigeria) (TOA Correspondent, 2020).

Sources of pharmaceutically active compounds in soil and sediment

Anthropogenic activities are primarily responsible for the discharge of pharmaceuticals into the environment (Daughton and Jones-Lep, 2011). This includes involuntary actions which are pharmaceutical excretion through the body or washing of topical medicines down the drain. Human pharmaceutically active compounds are excreted into the sewage system as a mixture of the parent compound and metabolites of the drugs, comprising mostly of transformation products and conjugated glucuronides. Conjugated compounds have been shown to be easily broken down during wastewater treatment, releasing the parent compound into the treated wastewater, and subsequently into the environment usually water bodies and soil (Ternes, 1998). In contrast, voluntary actions include the disposal of unused or out-of-date medicines down the drain or into refuse waste. Pharmaceuticals disposed of improperly into refuse waste enter landfill sites, where the unchanged bioactive compounds can leach into the soil. Agricultural medicines administered to livestock are also a source of pharmaceutical pollution.

Animal Excreta used as manure, containing the metabolite/unchanged pharmaceutical mix, is often used as a fertilizer, resulting in further exposure of these compounds to soil. Sludge from wastewater treatment plants (WWTPs) is also used as a soil fertilizer and may also be a source of pharmaceutical contamination in the environment. Soil leaching and groundwater recharge, caused by heavy precipitation, are the main modes of transportation for pharmaceuticals through the soil and into the aquatic environment. Other sources of pharmaceutical pollution of aquatic environment include industrial spills and aquaculture. The origins and pathways of pharmaceuticals into the aquatic and terrestrial environment are depicted in Figure 1.1

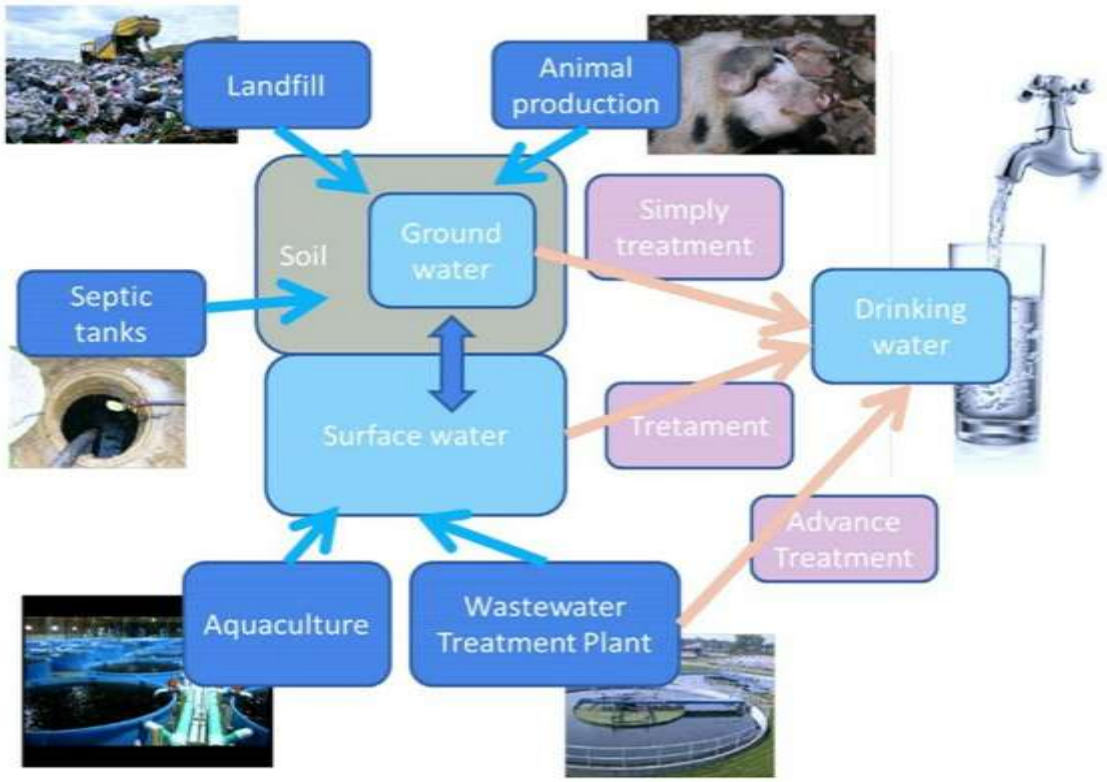

Figure 1.1: Pathways of pharmaceuticals in environment (Courtesy: McEneff *et al*., 2015).

The Landfill method of discharging refuse and industrial waste material is one of the pathways through which PHACs find their way into soil and ultimately into ground water as shown in figure 1.1. Consequently the uses of animal dung as manure also introduce PhACs into soil. According to the figure 1.1 (McEneff *et al*., 2015), even when surface water or waste water from homes and industries is treated very well , pharmaceutically active compounds are able to pass through into our drinking water.

In a study at Kapala, the capital of Uganda, the most detected PhACs studied frequently in the soil studied were carbamazepine, pyrimethamine and trimethoprim with concentrations in the range of 4.6-9-4 ng/g, 8.4-14.0 ng/g and 39.6 ng/g respectively (Bjorberg and Elenstrom, 2016). The author concluded that the cause of these PhACs occurring in soil was due to extensive use of wastewater for irrigation of crops.

Metabolism of PhACs in Soil and Sediment

What happens to PhACs in the environment such as river, sea and soil depends on many factors, such as the degree of transformation of the parent drug, the structure of the newly-formed metabolites, concentration of parent drug and metabolites excreted. Moreover the Pharmacokinetics of these drugs stipulates the processes by which the drugs are absorbed, distributed, modified and excreted by the body (Rosenbaum, 2011). Nonetheless,

pharmaceuticals are designed in such a way that the active ingredient can be released at a targeted site to give the required pharmacological effect. In order to enter into required organ or cell, pharmaceuticals must have lipophilic properties to pass through the cell membranes of the body. Metabolism is a process which requires many enzymes necessary for the transformation of lipophilic compounds to more polar metabolites suitable for elimination (Gumbleton, 2005). Though it is recalled as a deactivating process for most drugs, for pro-drugs, metabolism is considered as activating processes for pro-drugs, which release the active compound and produce a pharmacological effect (Rautio *et al*., 2008). Drug metabolism mainly takes place in the liver but other organs, such as the intestine, lungs and kidneys, and some microorganism in soil also have the ability to metabolize drugs .There are two main transformation phases which cause changes in compounds within the human body; the first Phase include reactions such as the addition or degradation of a reactive functional group on the parent molecule and the second Phase includes reactions where the parent compound and/or the Phase I metabolite are changed to a highly polar moiety (Andreozzi *et al*., 2003).

According to Magner *et al.*, (2015), in phase I as shown in figure 1.2 the pharmaceuticals represented as "R" are transformed by oxidation, hydrolysis or cyclization. Some of these modifications may be reversible when the substance reaches different treatment steps in the STP (Sewage treatment plant), which include both reductive degradation by anaerobic microbes and oxidative metabolism by aerobic microbes in environments. In the STPs the conjugated metabolites from the phase II metabolism are de-conjugated by bacteria back to the initial parent substances through enzymatic cleavage.

Figure 1. 2 (R = any pharmaceutical or organic compounds).

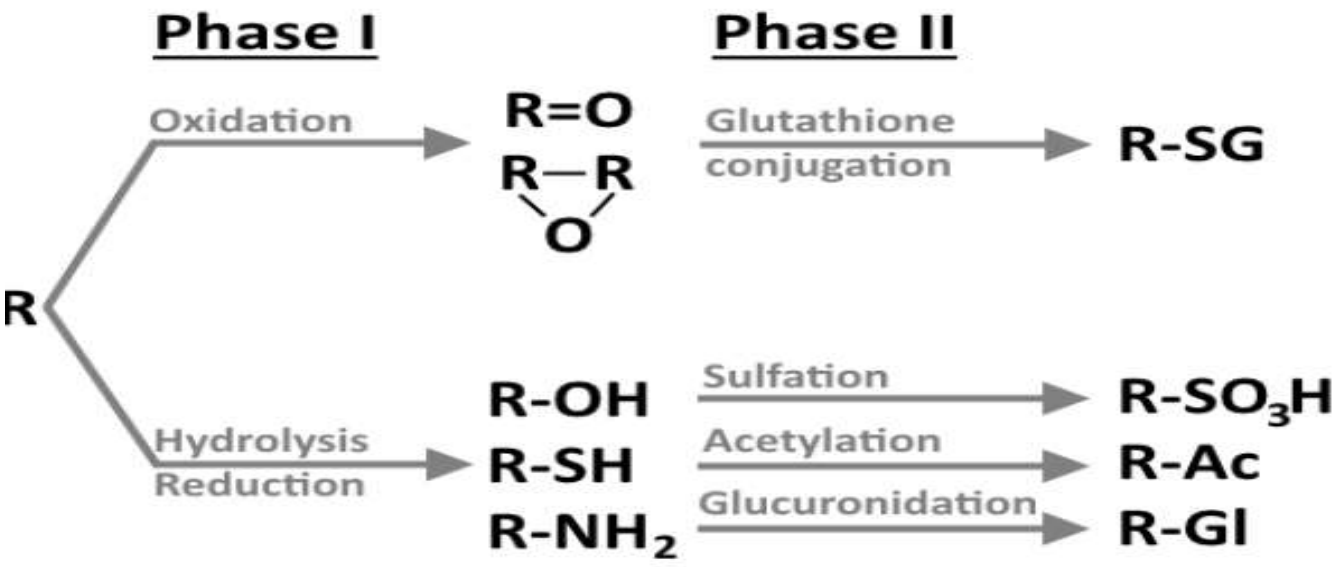

Figure 1.2: Phase I and II metabolism of xenobiotic (i.e. pharmaceuticals, denoted as "R" in the figure) in the liver (Courtesy: Magner *et al*., 2015).

From the figure 1.1, disposal of bio-sludge from STPs is the major pathways by which PHACs find their way into soil and sediments due to decongujations by micro-organisms in the soil. Within the soil, micro-organisms can also break down PHACS to even more dangerous metabolites as shown in figure 1.2.

According to a research by Hoff et al. (2016), sulfonamides such as sulfadoxine an antimalaria and N-acetylsulfapyridine are partially broken down in human body and also when excreted into sewage as unchanged sulfonamides or partly as their metabolites. It was also discovered that sulfonamides metabolites maintain their bioactivity and ecotoxicity of the parent substance (Garcia-Galon *et al*., 2012).

Fate and Removal of Pharmaceuticals in Environment.

The fate of pharmaceuticals in environment depends on their individual half-life. Whereas the pharmaceuticals with longer half-life pose more problems related to pharmaceutical pollution, other pharmaceuticals with shorter half-life are easily removed during waste water treatment (WWTP) stages. Conventional, primary and secondary sewage treatment involving coagulation/flocculation/sedimentation, successfully removes some PHACs, such as caffeine, ibuprofen and salicylic acid (Kimura and Watanabe, 2005). Other PhACs, however, such as the anticonvulsant carbamazepine, the lipid regulator gemfibrozil, the analgesic diclofenac and the drug metabolite clofibric acid are not successfully degraded completely in most WWTPs (Kimura *et al*., 2005; Lee *et al*., 2004) because of their lower nature of half-life in environment as shown in Table 1.2.

Table 1.2*:* Half-lives and wastewater treatment plant (WWTP) removal rates for PhACs **(Courtsey:** Doerr-MacEwen, 2007).

PhACs	**Half-life (days)**	**Reference**	**WWTP removal (%)**	**Reference**
Acetaminophen	3.11&4	Löffler, Römbke, Meller, & Ternes, 2005	>98 8.7	Ternes, 2001 Han, *et al.*, 2006
Amoxycillin			75 - 100	Castiglioni *et al.*, 2006
Atenolol			10-55	Castiglioni *et al.*, 2006
Bezafibrate			75 51 51 15-87	Ternes, 2001 Hua, *et al.*, 2003 Lindqvist *et al.*, 2005 Castiglioni *et al.*, 2006
Carbamazepine	No degradation1 1001 3281&2	Tixier, Singer, Oellers, & Müller, 2003 Andreozzi, Raffaele, and Nicklas, 2003 Löffler *et al.*, 2005	7 8 <40 0 91	Ternes, 1999 Heberer, 2002b Heberer & Feldmann, 2005 Castiglioni *et al.*, 2006 Han *et al.*, 2006
Ciprofloxacin	> 21 months3	Golet *et al.*, 2003	88 96 60-63	Golet *et al.*, 2003 Lindberg *et al.*, 2006 Castiglioni *et al.*, 2006
Clarithromyc in			0	Castiglioni *et al.*, 2006
Clofibric acid	No degradation1 1001 >41 1191&4	Tixier *et al.*, 2003 Andreozzi *et al.*, 2003 Packer, Werner, Latch, McNeill, & Arnold, 2003 Löffler *et al.*, 2005	51 0 0 30 80	Ternes, 2001 Heberer, 2002b Hua *et al.*, 2003 Castiglioni *et al.*, 2006 Han *et al.*, 2006
Diazepam	3111&4	Löffler *et al.*, 2005		
Diclofenac	5.01 81 <11	Andreozzi *et al.*, 2003 Tixier *et al.*, 2003 Packer *et al.*, 2003 06	0 69 17 21 26	Lee *et al.*, 2004 Ternes, 2001 Heberer, 2002b Hua *et al.*, 2003 Lindqvist *et al.*, 2005

			<15 24	Heberer & Feldmann, 2005 Han *et al*., 2006
EE2 (17□-ethinylestradiol)	812 3.0-7.73	Ying, Kookana, & Dillon, 2003 Colucci & Topp, 2001	85 ~0 65 76	Baronti *et al*., 2000 Ternes, 2001 Esperanza, *et al*.,2004
Enalapril			18-100	Castiglioni *et al*., 2006
Erythromycin			0	Castiglioni *et al*., 2006
Furosemide			8-54	Castiglioni *et al*., 2006
Gemfibrozil			5 50 69	Lee *et al*., 2004 Sedlak & Pinkston, 2001 Ternes, 2001
Hydrochlorothiazide			24-44	Castiglioni *et al*., 2006
Ketoprofen			18 78	Lee *et al*., 2004 Lindqvist *et al*., 2005
Ibuprofen	321 <61&4	Tixier *et al*., 2003 Löffler *et al*., 2005	87 99 90 60-70 67 92 38-93 78	Lee *et al*., 2004 Sedlak & Pinkston, 2001 Ternes, 2001 Carballa *et al*., 2004 Hua *et al*., 2003 Lindqvist *et al*., 2005 Castiglioni *et al*., 2006 Han *et al*., 2006.
Ifosfamide			~0	Kümmerer, *et al*, 1997.
Iopromide	7.6-69.31	Kalsch, 1999	0 0	Carballa *et al*., 2004 Hua *et al*., 2003.
Lincomycin			0	Castiglioni *et al*., 2006.
Naproxen	141 <11	Tixier *et al*., 2003 Packer *et al*., 2003	70 66 40-55 0 80	Lee *et al*., 2004 Ternes, 2001 Carballa *et al*., 2004 Hua *et al*., 2003 Lindqvist *et al*., 2005.

Norfloxacin			97	Lindberg *et al*., 2006.
Ofloxacin	10.61	Andreozzi *et al*., 2003	43-57	Castiglioni *et al*., 2006
Oxazepam	541&4	Löffler *et al*., 2005		
Oxytetracycline	1514	Hektoen, Berge, Hormazabal, & Yndestad, 1995		
Propranolol	16.81	Andreozzi *et al*., 2003	50 95	Sedlak & Pinkston, 2001 Ternes, 2001
Ranitidine			39-84	Castiglioni *et al*., 2006.
Salbutamol			0	Castiglioni *et al*., 2006.
Salicylic acid			98 >99 90	Lee *et al*., 2004 Ternes, 2001 Han *et al*., 2006.
Sulfamethoxazole	2.41	Andreozzi *et al*., 2003	60 17-71	Carballa *et al*., 2004 Castiglioni *et al*., 2006

In a recent study of the effects of sewage treatment on 55 pharmaceutical agents, Ternes (1998) found an average pharmaceutical removal rate of approximately 60% for a German WWTP using clarification, aeration and addition of Fe (II) chloride which ultimately reduced the half-life in days of pharmaceuticals determined. According to Castigioloni et al., (2006), as shown in table 1.2 amoxicillin was 75-100% removed from the waste water treatment plant. In same study, amoxicillin was not detected in effluent from WWTP but was detected in the influent from home and industries.

Removal rates are highly not specific to all pharmaceuticals; however, depending on the specific operating parameters of individual wastewater treatment plants (Tauxe-Wuersch *et al*., 2005) and half-life of pharmaceuticals in different environmental media. The changes of operating parameters of conventional, sludge-activated wastewater treatment plants, particularly the solids or sludge retention time (SRT) can increase the removal of some microbially-degraded pharmaceuticals such as bezafibrate, but PhACs resistant to microbial degradation, such as carbamazepine, will not optimized by modification of operating parameters of the SRT (Clara, *et al*., 2005). According to Clara *et al*, (2005) using membrane bioreactors can also increase removal of microbially degradable PhACs by allowing higher SRTs within a low-volume syste. Presence of Nitrifying bacteria in WWTP may help to remove some of the more polar PhACs (Eichhorn *et al*., 2005). Treatment methods relying on microbial degradation which usually occur at the secondary treatment stages utilizing activated sludge, are extremely sensitive to seasonal variation, as decreasing temperature by 10^{o}C halves the degradation rate (Clara *et al*., 2005). Vieno, *et al*., (2005) discovered that removal of PhACs in Finnish WWTPs decreased by

25% on average in the winter. Including the opeating Performance of WWTPs in terms of plant parameters such as BOD, COD, and nitrogen removal is a good indicator of capacity to remove PhACs (Clara *et al*., 2005; Vieno *et al*., 2005) as can be seen in the table 1.0.

Effects of pharmaceuticals in environment.

As it was reported by Brian *et al.* (2004), mixtures of different drugs can have a "cocktail effect" a situation whereby adverse effects are manifested when two or more different drugs are mixed together. For example, pharmacists and doctors always warn patients that they should not mix ibuprofen with beta-blockers. But a fish swimming in a soupy mixtures of drugs, and other chemicals in a polluted river and other water ways, have no other choice but to swim in it every day (Brian *et al*, 2009). The cocktail effect on fish could be disastrous owing to the fact that extent of drugs usage is increasing everyday as human population continues to age.
Another profound effect of pharmaceutically active compounds on aquatic organisms is disruption of endocrine hormone such as feminization of male fish. The presence of estrogen and other hormone like drugs cause feminizing of male fish thereby drastically reducing their population as shown in the figure 1.3.

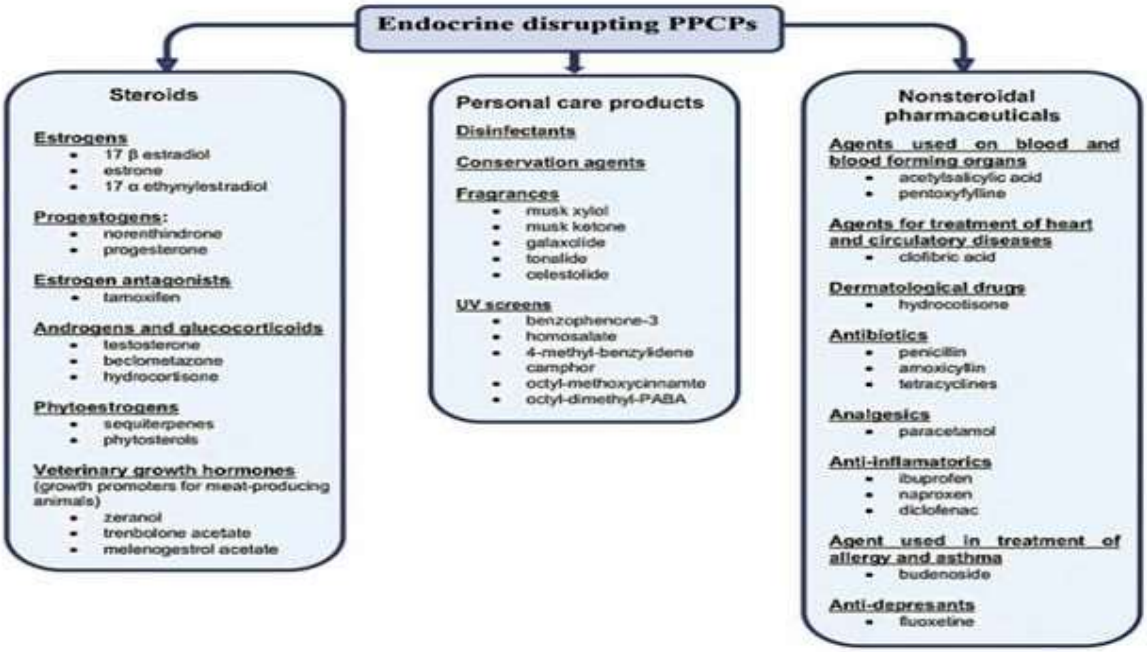

Figure 1.3: The schematic diagram of pharmaceuticals and other organic compounds as endocrine disrupting compounds (Courtesy: Ebele *et al.*, 2017).

Exposure of vultures in India between 1996-2004 to an anti-inflammatory drug diclofenac drove the birds to almost being extinct (Green *et al*., 2004). The diclofenac was administered to cattle to treat pain and fever, and because people in India do not eat beef, the carcasses of dead cattle were left for the vultures to feast on, together with cattle given high doses of diclofenac before their death the vultures were both affected as a result of bioaccumulation and bio-concentration

of diclofenac. According to the test conducted by Cuthbert *et al*.,(2011), it turned out that vultures from the genus Gyps are particularly sensitive to diclofenac and that time alone, between 10-40 million vultures died from abdominal gout and acute kidney failure. The effect of this almost caused population crash of the vulture.

According to 2014 report by UK water Industry Research, it was found that in most of 160 sewage treatment works studied, many common drugs were found in the final effluent in concentrations high enough to potentially affect ecosystem (Browne et al., 2014). The drugs found in the research were the anti-inflammatory ibuprofen and diclofenac, the antibiotics erythromyn and oxytetracycline and the female sex hormone 17b-estradiol.Another pharmaceutical pollution is caused by the release of active ingredients into nearby waterways, which ends up creating localized hotspots pollution.

Methodologies Applied in Detecting and Measuring Pharmaceuticals in Soil Sediment Sample.

Instrumental analytical techniques for pharmaceuticals analysis in environmental samples used in detecting and measuring pharmaceuticals in environmental sample are very important because of very low concentration of these compounds in environment. According Krogh et al., (2008), the major challenge in the study of pharmaceuticals in environment has been that they are not easily detected and qualitatively analyzed.

In order to qualitatively detect and measure the quantity of PhACs in environmental samples different techniques are always applied as shown in the following heading 1.8.1.

Concentration and Cleanup of Pharmaceuticals in soil and sediment extracts using Solid Phase Extraction

According to Perez-Lemus *et a.,l* (2019), UAE and MAE were the most common method used to extract pharmaceuticals from environmental sample. The pharmaceuticals in sediment and soil samples extracts were concentrated and cleaned up using the method reported by Babić *et al.*, (2006) which was also used on waste water and surface water. In their method, hydrophobic lipophilic balance (HLB) sorbents (SPE cartridges) were used in extraction of pharmaceuticals from wastewater, and surface water. HLB sorbent is chosen for multi-residue extraction due to mixed chemistry and because it has shown good performance in extracting a mixture of acidic and basic pharmaceuticals (Löffler *et al*., 2005).

To analyze pharmaceutical pollutants coexisting in soil, river and sewage sediment samples along with many other substances in concentrations in the range from ng/L to μg/L, samples need to be concentrated to the level of concentration which is equal or above detection limit of Liquid chromatography connected to mass spectrometry, LC-MS and LC-MS/MS or other instruments (Lishman *et al*., 2006). Even though LC-MS/MS has high sensitivity and superior selectivity, impurities in the samples can interfere with the ionization of the target substances and thus drastically lower the sensitivity and accuracy of the analytical method.

The solid sample, in this case, sediment and soil are grinded and sieved in order to have a homogenous sample. Soxhlet, microwave assisted extraction (MAE) or ultrasound assisted extraction (UAE) is applied to first extract the pharmaceuticals into a liquid Supernatant upper layer after centrifugation. The pre-concentration and cleanup are performed using any of the followings: liquid extraction (LLE), solid phase extraction (SPE) (Azuma *et al*., 2013), solid phase micro extraction (SPME) etc. If derivatisation is not required, the pharmaceuticals are analysed after analyte extraction and clean up usually by using liquid chromatography (LC) or LC-MS/MS.

Azuma *et al*., (2013), discovered that it is highly important to clean up impurities from the samples during preparation using a common method like SPE. SPE is a sample preparation process based on the separation mechanism of column chromatography. In SPE, a sample solution is passed through a column containing selective stationary adsorbent. The target substance is retained in the adsorbent, the impurities are washed and removed, and the target substance is eluted from the adsorbent with a solvent and collected. SPE is a superior method that is not only simple and fast but also uses a very small amount of solvent for extraction. It has superior purification and reproducibility, and can process many samples simultaneously and more efficiently than with liquid phase extraction, which is a liquid-liquid separation method that uses organic solvents to extract target components. A wide variety of materials are used as the SPE stationary phase, beginning with the C18 stationary phase (Olkowska *et al*., 2012) and a stationary phase with ion exchange groups (Kovala *et al*., 2009).
The stepwise method of SPE application is shown below.

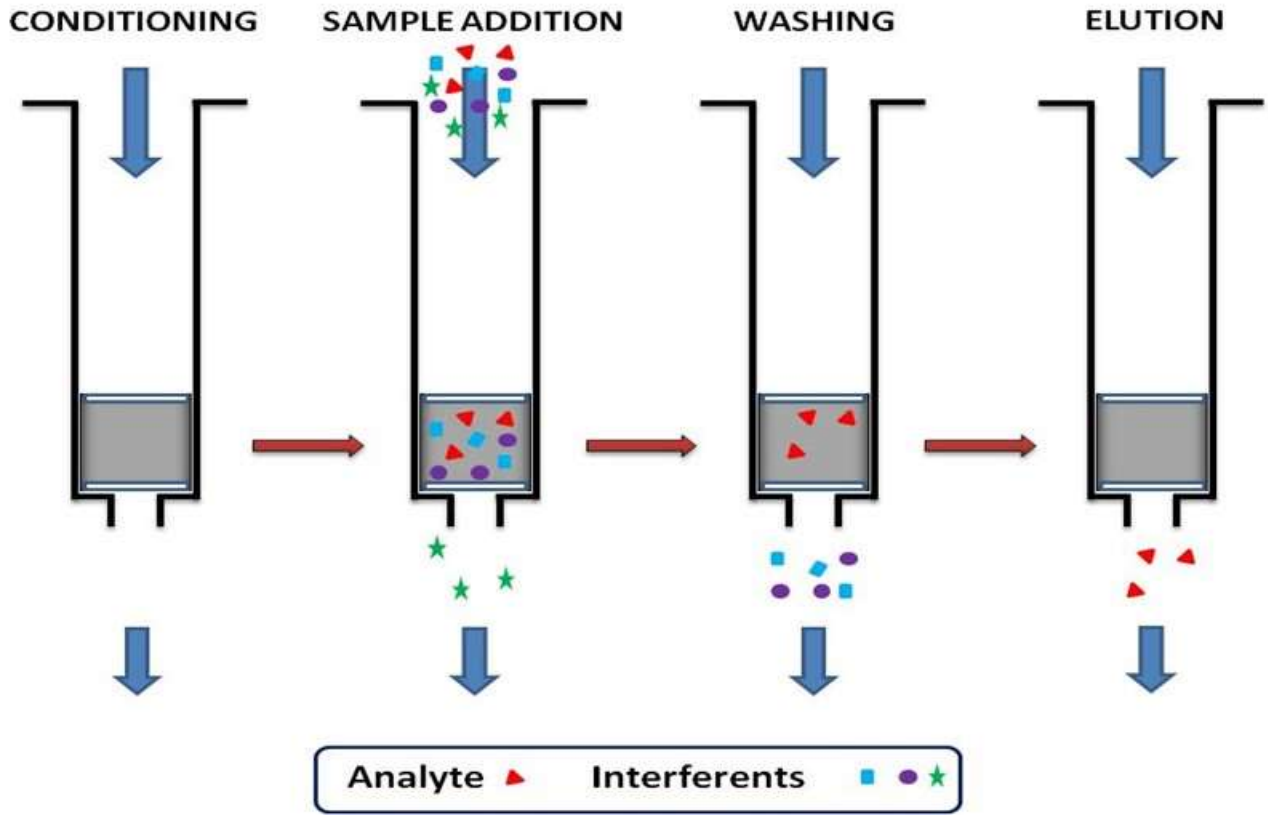

Figure 1. 4: Stages of solid phase extraction (Courtesy: Lucci *et al.*, 2012)

For instance: the recent study used SPE for simultaneous determination of four representative antiinfluenza drugs, oseltamivir phosphate, oceltamivir carboxylate, zanamivir and amantadine by combination of strong-cationic SPE cartridge and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Mu *et al*, 2016). The major precaution was that Special care must be taken for selection of the adsorbent to make the recovery percent higher because of the difference in adsorption- desorption profiles even if the same type of ion-exchanger are used. The extraction mixture was MeOH/H2O (1:1 v/v) and the operating temperature and pressure was 100°C and 1000 psi respectively according to recent research by (Nong *et al.*, 2014) . sdExtracts were dried at 60°C and stored at 3°C before liquid chromatography analysis (Matongo *et al*., 2015).

Statement of Purpose

As it was noted by Ebele *et al.*, (2017) in their study, Currently, very little is known about the occurrence, fate and behavior of pharmaceutical and personal care products (PPCPs) in the African environment. According to the same author, in most developing countries in Africa, where the waste disposal system is basically through landfill, it is pertinent to monitor the presence of PPCPs, because some of these PPCPs are not easily degradable either through biodegradation or photo degradation. Moreover, they can contaminate groundwater which

constitutes a major water supply for a large proportion of the population in arid regions of Africa.

Thus, there is a need for proper documentation of existence of PhACs in developing countries like Nigeria, which is the main objective of this thesis, to forestall the challenges of many complications due to the presence of PhACs in the environment. This does not stipulate that Pharmaceuticals should be banned because of their potential environmental impacts. Rather, it means that academics, scientists and members of the pharmaceutical industry should begin to carry out risk assessment of the presence of commonly used drugs and also develop strategies to address the issue of PhACs in the environment now, instead of waiting several more years until the degree of environmental damage primarily caused by PhACs can easily be felt.

To this end, following the fate and effects of pharmaceutically active compounds in environment, one of it being that PhACs in environment are the prime cause of antibiotics resistance by microorganisms as being discovered in the research conducted by Stalin *et al.*, (2016), there is a need for proper investigation of presence of PhACs in Nigeria and Lagos in particular being Nigeria's most commercial hub.

The Aim and Objectives

The aim of this study is to investigate the presence of some pharmaceutically active compound in soil and sediment around selected drug manufacturing companies in Lagos.

The Specific Objectives include:

(1) To determine the physico-chemical parameters of soil and sediment affected in the study areas.
(2) To determine presence and concentration of PhACs in these samples.
(3) Ascertain the possible link between the detected PhACs and activities / products of Pharmaceutical companies.

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LITERATURE REVIEW

Review of Recent Studies on Pharmaceuticals in Environmental Media (Soil and Sediments)

The study of pharmaceuticals in environment has been at forefront of environmental research recently because of better development of analytical instruments. These analytical instruments make it possible for ultra-trace analyte determinations which could not have been possible with classical methods of analysis. It was mentioned that analysis of pharmaceuticals in soils, water and sediments of aeration ponds is a growing knowledge about the impediments of these pollutants even at ultra-trace amounts and their mixture effect of these pharmaceuticals in environment (Brian *et al*., 2004).

The Chemical Structures of the selected pharmaceuticals to be Detected and Quantified

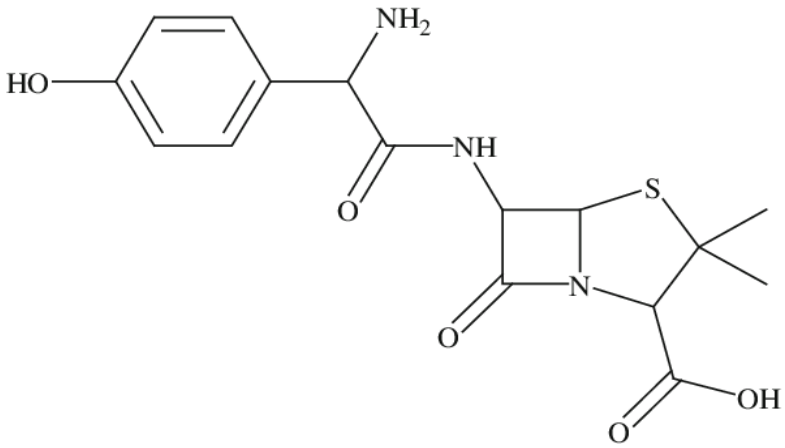
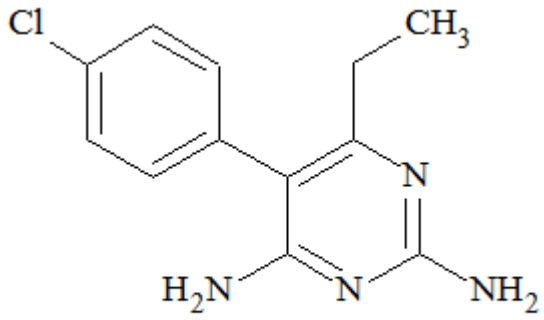


Figure 2.1: The chemical structure of Amoxicillin (Courtesy: Panizza *et al*., 2014).

Structure of Sulfadoxine and pyrimethamine (antimalaria)



Molar Mass: 248.71

Figure 2.2: The chemical structure of pyremethamine (Courtesy: Mohamed *et al.*, 2016)

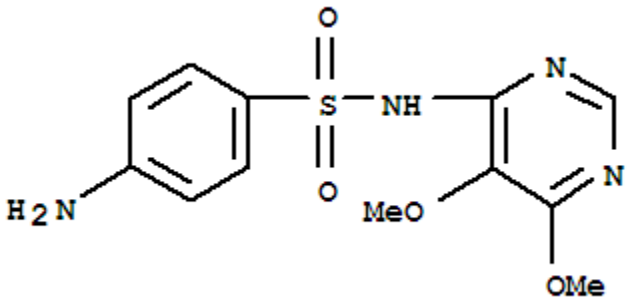


Figure 2.3: The chemical structure of sulfadoxine (Courtesy: Ngobiri *et al.*, 2017)

The antimalarial drugs pyrimethamine and sulfadoxine contain benzene ring and other aromatic ring which are attributed to their higher stability in environment. In a recent study by Ngobiri *et al*. (2017), pyrimethamine and sulfadoxine were used as anti-corosive agents because of high stability in acidic medium. Pyrimethamine and carbamazepine were observed to have the highest average concentrations amongst the pharmaceuticals determined. The two drugs being most frequently detected could last longer in soil compare to other pharmaceutically prepared drugs (Bjormberg and Elenstrom, 2016).

Sample Preparation and Analysis: a Review for Pharmaceuticals Determinations

Different sample preparation methods have been applied on sediments from river or seas sediments and soil to make it possible to analyze the existing pharmaceuticals in the samples. In a recent study by Matongo *et al.* (2015), the sediments from river were air dried and homogenized before they were subjected to extraction using Ultrasounds assisted extraction (UAE). 50 gram of samples were used in other to increase the concentration of analyte to be more than limit of quantification of HPLC detectors. EDTA was also added in the method developed by Shraim *et al.*, (2012) as metal chelators.

Although, there are many traditional sample-preparation methods used in concentration and cleanup of interfering matrixes for the analysis of pharmaceuticals in sediments and soil samples, solid phase extraction (SPE) is the most commonly used extraction technique for the analysis of pharmaceuticals in Supernatant solution after UAE or MAE. This technique allows for analyte concentrations and clean-up, both of which are necessary to improve the sensitivity of detection. Another advantage of using SPE is that, all the steps (extraction and cleanup for mainly liquid samples) can be carried out at the same time, which makes the analysis less time-consuming.

In a study conducted by Vazguez-Roig *et al.* (2010), a sensitive analytical method was proposed based on pressurized liquid extraction (PLE), and pre-concentration by solid-phase extraction (SPE), followed by liquid chromatography-electrospray tandem mass spectrometry (LC-ESI-MS/MS) for the determination of seventeen pharmaceuticals in soils and sediments. The method

was based on sample homogenization and the use of Na-EDTA to wash soil before extraction and the extraction was performed with water at 90 degrees C. Special emphasis was placed on the optimization of the extraction procedure to develop a green method that reduces, at a maximum, the use of organic solvents in order to eliminate matrix components during the clean-up. The proposed method gave a result which was linear in a concentration range from 0.3 to 333 ng/g, with correlation coefficients higher than 0.993. Their concentrations ranged from 0.1 to 6.8 ng/g and from 0.25 to 23 ng/g, respectively. In the same study, acetaminophen, carbamazepine, ciprofloxacin, clofibric acid, codeine, diazepam, fenofibrate, metropolol, ofloxacin and propanolol were detected at concentrations from MDL to 35.62 ng/g in soils and sediments from marsh areas. Due to the low recoveries using the proposed method, results for fenofibrate and diclofenac could only be considered as semi-quantitative (Vanguez-Roig *et al*., 2010).

Pharmaceuticals in Industrial Waste Water and River Sediments Impacted by Nearby Pharmaceutical Industry

In a study of river water from the Mekong Delta, Vietnam, the levels and distribution of 12 antimicrobials were tested. In this study, a few compounds such as sulfamethoxazole, sulfamethazine, trimethoprim and erthromycin were detected at concentration ranging from 7 to 360 ng/L (Larsson *et al*., 2007). Comparing their findings of antimicrobials with another recent study of Japanese Urban River, sulfamethoxazole, sulfapyridine, trimethoprim, erthromycin were found at concentrations ranging from 4 to 448 ng/L (Managaki *et al*., 2007). Extremely high concentrations of pharmaceutical ciprofloxacin was found up to 31 mg/L in the effluent from a WWTP impacted by drug manufacturing waste water in Patanchem, near Hyderabad India (Stalin *et al*., 2017). The concentrations of these PhACs in river water were also discovered to have a good correlation with their concentrations in sediments.

According to recent study by Matongo *et al*., (2015), clozapine was detected in both surface water and sediment. In same study, a higher concentration was observed in surface water compare to sediment.

Review of Analysis of Pharmaceuticals in the Soil and Sludge from STP (WWTP)

According to the study by Magner *et al.*(2013), the soil samples which were not treated with sludge showed no detectable levels of investigated pharmaceuticals. The soil samples from land treated with STP /WWTP sludge showed detectable levels of up to 4 of investigated pharmaceuticals between 0.4 to 4.9 ng/g dry weights. The composite soil samples collected at large depth below 0.3-0.6 m revealed no detectable levels of pharmaceutically active compounds investigated (Magner *et al*., 2013). Thus, the deeper one goes in the soil, the more likely to get no pharmaceutically active compounds. The authors concluded that the soil exposed to sludge on the fields showed a general higher mobility of pharmaceuticals with acidic Chemical properties compared to neutral and basic pharmaceuticals which agreed with the Findings by Wu *et al.*, (2014). In another study by by Matongo *et al.*(2015) among the investigated antipyretics, acetaminophen was detected in both the effluent and bio-solid. They generally discovered that higher concentration was observed in the sludge up to 7.76 µg/g compare to its concentration in waste water (Matongo *et al*., 2015). Acetaminophen concentration in effluent was less than its

concentration in influent because of its high removal efficiency in the WWTP is lower than that reported elsewhere (Tora and Kikuta, 2005).

Analytical Challenges in the Determination of Pharmaceutical Residues in Soil Samples

Though there has been an improvement in analytical chemistry, many pharmaceutical compounds are more easily detected in surface water and wastewater environmental media at ppm level but not at lower concentrations like part per trillion, ng/L (Białk-Bielinska *et al*., 2016).Thus at very low concentration usually part per trillion, pharmaceuticals become difficult to be detected or determined. According to recent findings by (Magner *et al*., 2016), a different situation was depicted due to soil matrix effects and availability of analytical methods for determining drugs in soil matrices.

The matrix effects on pharmaceutical analysis were studied by Magner et al. (2016), as shown in Table 2.1.

Table 2.1: Matrix effects of pharmaceuticals analyzed in sludge (Magner *et al*., 2016).

Substance	Total Recovery %	Loss to ion Suppression	Loss in Recovery
Diclofenac	12	82	6.3
Furosemide	8.3	62	29
Hydrochlorothiazide	60	9.8	30
Ibuprofen	9.7	85	5.4
Naproxen	15	75	9.7
Ramipril	41	6.6	52
Warfarin	66	15	20
Atenolol	31	12	57
Amiodipine	20	65	15
Bisoprolol	65	2.4	33
Caffeine	48	29	24
Carbamazefine	25	59	16
Citalopram	78	-46	68
Fluoxetine	19	62	19
Ketoprofen	11	80	8.6
Metoprolol	77	-19	42
Oxazepam	13	74	13
Paracetamol	41	11	48
Propranolol	56	11	33
Ranitidine	0.7	99	0.8
Risperidone	49	26	25
Sertralin	25	25	50
Simvastatin	7.2	90	3.0
Terbutaline	44	4.5	52

Average:	**34**	**38**	**27**
Median:	**28**	**27**	**24**

From the table above, the effects usually reduce the overall percentage recovery as shown in the table, thus far making the amount of analyte to be below the real concentration in the sample. Its effect was observed by recovery losses during sample preparation as a result of ion suppression or ion-enhancement, during mass spectrometer analysis in case of HPLC –MS (Magner *et al*., 2016).

In the recent past, many methods have been developed for the analysis of pharmaceuticals in aqueous matrices; however, only limited published papers exist for the determination of drugs in soil matrices.

In the past ten years, different ways of analyzing pharmaceuticals have been proposed for the monitoring of pharmaceutical residues in soil samples. However standardized methods for the identification and quantification of many pharmaceuticals in soil samples have not yet been developed fully as standard (Kümmerer, 2003). The interest bothers on the therapeutic classes as antibiotics, analgesics/anti-inflammatory drugs, hormones, liporegulators, beta-blockers, anti-epileptics and antidepressants which are best analyzed using different methods (Monteriro and Boxall 2010), but the number of chemical compounds used as human and/or veterinary drugs is estimated over 4000 molecules and 10,000 products. Interestingly anti- helmintics as well as the antibiotics belong to the most obviously used veterinary drugs. Only limited published papers are available concerning the determination of anti-helmintics in the soils and only few papers have dealt with the environmental fate of these drugs in the soils (Kolar and Erzen 2006). As Białk-Bielinska *et al*. (2016) put it, in tandem to the aforementioned facts, there is still a need for development of required analytical methods in research of the occurrence and fate of pharmaceuticals in sediments and soil environments. Only the analytical methods which are very sensitive, accurate and easy to apply in routine analysis will meet reliable risk assessments of the presence of pharmaceuticals in soil matrices can be made. This has been made so imperative for the development of such methods.

Although the Sample preparation techniques are very important in all the applicable methods, the efforts in pharmaceuticals identification and quantification have been primarily focused on optimization of the sample preparation, extraction and clean-up steps for removal of interfering chemical species and the enhancement of the environmental safety of these procedures (Białk-Bielinska *et al*., 2016). Thus far, optimization of the available sample preparation methods is a pressing challenge for accurate quantification of pharmaceuticals. However, there is a need for development of on-line methods, automatic or semi-automatic protocols for these methods. Recently, the proposed analytical procedures for detecting and determining pharmaceuticals are mainly based on HPLC–MS/MS and less frequently on GC–MS. This is because pharmaceuticals as organic compounds can easily be degraded or destroyed on heating to be volatilized in GC-MS. The main development in HPLC–MS or HPLC-MS/MS was to combine

powerful MS detectors with modern chromatographic approaches such as UHPLC, GC or HPLC. This kind of methods has allowed the development of multi-analyte techniques for the detection of a wide range of drugs in a single analytical run. The major disadvantage, however, of these methodologies was the need for complex equipment and the high costs of analysis. Therefore it is very important to develop low cost methods based on microbiological, immunoassays and biosensor for pharmaceuticals in soil and other environmental samples.

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MATERIALS AND METHOD

Sample Location Description.

Ologe Lagoon passes through highly industrialized areas and receives runoff from rural communities and the industrial /municipalities WWTP effluent along its course as well as from agricultural areas. These contribute to the levels of pollutants in the water. The resident area is along the Ologe Lagoon basin which is also very close to heavily industrialized Agbara Estate. Isolo canal passes through the area where Pharmaceutical Company is located and residential area are located along its basin.

Four sampling sites were purposely selected to represent various anthropogenic activities taking place at Agbara area very close to Aghara Estate housing many industries including pharmaceutical industries and Isolo area which houses the pharmaceutical industry as shown in figure 3.2, two sampling sites for each.

Global Positioning System (GPS) was used to verify the location of each sampling point for future reference. The sampling site coordinates, site activities and nature of sites during the sampling season are presented in the Table 3.1 and the maps of sampling sites are given in figure 3.1 and 3.2.

Tables 3.1: Sample location description and site activities.

Sampling Sites Code	Nature of site	GPS coordinates of sampling sites.	Site activities
OLS	Ologe Lagoon sediment	6.498769-3.102846	Dredging area
ARS	Agbara Residential Area soil, nearest to borehole water	6.500011-3.102476	Local residence water supply
ICS	Isolo Canal Sediment	6.543154-3.332576	Closed to Pharmaceutical company
IBS	Isolo (Borehole) residential area soil nearest to water bore hole	6.543810-3.332367	Residential area water supply

Figure 3.1: Map of Ologe lagoon at Agbara Lagos State

Figure 3.2: Map of Isolo Canal at Ajoa st, Isolo Lagos State

List of Pharmaceuticals

A subset of 3 pharmaceuticals was selected for the analyses as shown in table 3.2. The selected substances represent a commonly used base set of pharmaceuticals which are easily got in local pharmaceutical shops in the study areas. With their wide range of chemical properties they represent two different classes of pharmaceutical substances: the antibiotic and antimalaria drugs. This helps to select the three drugs for the current study since it is not possible to perform studies on all of the thousands of pharmaceuticals that exist in the market today.

Table 3.2: List of selected pharmaceuticals and their type

Pharmaceuticals	**Type**
Amoxilin	Antibiotics
Sulfadoxine	Antimalarial
Pyrimethamine	Antimalarial

List of some drugs manufactured by nerby pharmaceutical companies around the sampling sites

The list of some pharmaceutically prepared drugs with their brand names, manufactured by nearby pharmaceutical companies around sites where samples were collected include the followings:

1. Maldox containing the active ingredients: sulfadoxine and pyremathemine
2. Emzoclav containing the active ingredients: amoxicillin and clavulanic acid.
3. Emmox Containing amoxicillin

Sample Collection

River sediment and soil were collected in a ziplock polythene bags, which were washed with phosphate-free soap, rinsed with tap water and distilled water, and finally rinsed with HPLC-grade acetone and n-hexane to eliminate polar and non-polar contaminants prior to sampling. The soil of the Agbara resident area was collected around water borehole and Ologe Lagoon sediment was collected by scooping approximately 0-6cm of river bed to represent the control sample and the sample likely to be affected by the discharge of industrial/Municipal waste water and slugde from WWTP respectively. On the same day, the sediment of Isolo Canal and the soil around borehole water system at residential area were collected. The samples were immediately packed in a container placed in black polythene bag to be transported to laboratory.

Samples were air-dried in the laboratory and thereafter were kept in the fridge at 4 °C until extraction following the method described by Kim *et al.* (2007). At each site, one batch of sample was taken between January to March on a monthly basis and all samples were extracted within few weeks of sample collection.

Determination of Sample Physico-Chemical Properties.

In order to relate the nature of samples to the pharmaceuticals, detected in soil and sediments, the following physco-chemical measurement were done, Vis.

1. pH of samples
2. Conductivity of the samples.
3. Total organic carbon (TOC)
4. Cation Exchange capacity (CEC).

pH Determination and Conductivity

pH, conductivity were determined with a hand-held meter HANNA pH meter (Model: HI 98129, Hanna Instruments, California, USA) using a dilute solution of calcium chloride of each samples according to the used by Houba et al. (2000). For the pH, the electrodes on the instrument were first dipped into two different solutions of buffers at pH of 4.0 (acid pH) and 9.0 (alkaline pH) before placing them into the samples that have been thoroughly mixed with 0.01M calcium chloride, to take readings. The pH probes were rinsed with deionized water before another sample reading was taken.

Total Organic Carbon Determination

Total organic carbon was determined using the standard titrimetric method (Admoroti , (1996). The basic treatment of samples was addition of potassium dichromate with shaking followed by addition of 20 ml concentrated sulfuric acid. The mixture was allowed to stand for 30 minutes. 200 ml of water was later added to the mixture followed by addition of 10 ml concentrated phosphoric acid. After addition of 3 drops of ferrion indicator, the titration with ferrous ammonium sulphate (FAS) was performed until wine red end point. The same treatment was done on blank solution without the sample.

The expression for computation of TOC (total organic carbon content) of the samples is given as;
mg total organic carbon /g sample = (Vb -Vs) * M* 16000/(mass of sample in gram)
Vb = volume of FAS used on the blank to reach end point.
Vs = volume of FAS used on sample to reach the end point.
M= concentration of Fe^{2+} in mol/dm^3.

Determination of Cation Exchange Capacity of Sediment and Soil Sample.

Using titration method, 2 g of the soil sample was weighed into a 15 mL centrifuge tube and 10 mL of 0.5 M magnesium acetate of pH 7 added as reported by Mohamed *et al.,* (2005). The mixture was shaken for 5 min to saturate the soil sample with magnesium, centrifuged for 5 min at 2000 rpm and the supernatant discarded. This step was repeated 3 times. Then, 10 ml of 0.25 M magnesium chloride was added and the mixture shaken for 1 min, centrifuged for 5 min and the supernatant discarded. 10 ml of 1:2 water to acetone solution was then added and the mixture shaken, centrifuged and the supernatant discarded. Thereafter, 10 mL of 0.25 M sodium chloride solution was added, shaken for 1 min, centrifuged for 5 min at 2000 rpm. This step was repeated 3 times and the supernatant saved for the magnesium test in a 250 ml conical flask. Then, 10 ml of ammonium chloride-ammonium hydroxide buffer, 2 drops of Erichrome black T, 5 drops of

methylred together with 10 drops of 10% sodium cyanide were added and titrated with 0.25 M sodium salt of ethylenediaminetetraacetic acid solution to a greenish end point.

$$\text{CEC (meq/100g)} = \frac{\text{Meq Mg titrated x 100 g}}{\text{Weight of soil}}$$

Meq Mg titrated = volume of Sodium ethylenediaminetetraacetic acid used to reach end point.

Sample Preparation for Pharmaceuticals Analysis

Sediment (or soil) samples were extracted using a method reported by Vazquez-riog et al., (2012) with modification. Briefly, 5 g of sediments were extracted first with double distilled water in an ultrasonic bath. Thereafter, mixture of methanol, acetone and water in the same proportion was successively used to extract the pharmaceuticals twice .The slurry was shaken in ultrasonic bath for 10 minutes at 30ºC before being centrifuged (DuPont instruments SS-automatic centrifuge) for 5 minutes at 2000 rpm to separate out a clear supernatant upper layer. Filtrate got using water during first extraction was added to the supernatant solutions and the resulted liquid was air-dried until only aqueous solution was left. The obtained sediment extracts were diluted to 100 mL with double distilled water.

Concentration and Clean-up of Pharmaceuticals in the Soil and Sediment Samples Extracts.

Samples were extracted using solid phase extraction with HLB Oasis its conditioning. The SPE (Supelco C18 catridge in 6 ml tube) cartridges were conditioned with 5 ml methanol and 5 ml water adjusted to pH 3.0 with phosphate buffer. 100 ml of liquid extract was loaded onto the cartridge after adjustment of the pH to 3.0 with phosphate buffer solution. The pH 3.0 was chosen as it was the best optimized pH for pharmaceutical extraction from water (ground, surface and waste). 4 ml of 0.01 M sodium salt of etheledia minetetracetic acid (EDTA) to get rid of metal ions which could be chelated by the available PhACs. The flow rate was maintained at 0.6 mL/min. Subsequently, the solid phase was air-dried completely for 30 min, and Analytes were eluted with (1×10) ml of a mixture of 5ml methanol and 5 ml acetonitrile followed at flow rate of 0.6 mL/min. Eluates were evaporated to dryness under exposing them to air and re-dissolved with 1 mL of methanol.

Preparation of Analytical Standard Chemicals

Pharmaceutical Standards of amoxicillin, sulfadoxine, pyrimethamine were purchased from Sigma-Aldrich. Ultra-pure water, which was purified using Eli Millipore Water system, was used in preparation of standards. Acetic acid, ammonium solution, methanol, acetonitrile, acetone and ethyl acetate were purchased from Sigma-Aldrich. All reagents applied in analysis were of HPLC-grade. 0.01 g of each drug as standard compounds was used to make Stock solutions (1000 ppm) by dissolving in 10 mL of 50:50 (v/v) methanol and Millipore water. The resultant solution was stored in the fridge at 4 °C until analysis (within a week of preparation).

Standard mixtures, at different concentrations, were prepared by appropriate dilution of the stock solutions and consequently mixing them together. The mixture was hand shaken and stored in the fridge at 4 °C until analysis. These were used as external calibration of HPLC over a range of 0.1□100 µg/L. The two concentrations used were 25 ppm and 50 ppm of amoxicillin, pyrimethamine and sulfadoxine. Limits of detection were calculated using a signal to noise ratio of 3, whereas limits of quantification were calculated using signal to noise ratio at 10.

Detection and Quantification of Selected Pharmaceuticals

Quantification of pharmaceuticals in the soil and sediments was performed using HPLC Agilent 1200 series of reverse phase Zorbax C18 (100 × 2.1 mm, 3.5 µm) column for separation and quantification of the target analytes as it was used by a study elsewhere (Matongo *et al*., 2015). The target analytes were eluted by an isocratic method using a mobile phase composition of 60% phosphate buffer and 40 % acetonitrile. The mobile phase was allowed to flow constant flow rate of 2 ml/min. The column temperature was kept at 30 °C. An injection volume of 1ml for each sample extract was used for all the analysis. The pharmaceutically active compounds (amoxicillin, pyrimethamine and sulfadoxine) were monitored at 254 nm using UV detector.

RESULTS AND DISCUSSION

Results and Discussion of Physic-chemical Analysis of Soil and Sediment Samples

The tables below contain the results of the following physic-chemical parameter: pH, Conductivities, Total organic carbon and cation exchange capacity. The results of these parameters are placed according to the month of the samples collected.

Table 4.1: Physico-chemical result of the first sampling event (1ST month)

Sample code	$pH_{1:5CaCl}$	Conductivity (uS/cm)	TOC %	CEC (Meq/100g)
OLS1	7.2	1.73	1.61	5
ARS1	7.0	0.98	2.12	25
ICS1	6.5	2.05	3.52	35
IBS1	6.6	1.6	4.60	34

Table 4.2: Physico-chemical result of the first sampling event (2nd month)

Sample code	$pH_{1:5CaCl}$	Conductivity (us/cm)	TOC %	CEC (meg/100g)
OLS 2	7.4	1.76	0.396	6
ARS2	7.2	1.77	1.38	18
ICS2.	7.1	2.06	0.828	16
IBS2	6.7	2.28	4.14	30

Table 4.3: Physico-chemical result of the first sampling event (3rd month)

Sample Codes	$pH_{1:5CaCl}$	Conductivity (us/cm)	TOC %	CEC (meg/100g)
OLS3	7.4	1.76	0.95	7
ARS3	6.4	1.25	2.07	22
ICS3	7.6	0.19	2.42	23
IBS3	7.3	1.77	2.84	25

The pH and conductivities of the soil and sediment samples were carried out in a dilute calcium chloride solution. This method has been a standard method to stabilize the content of soil solution and to release all available hydrogen ions which might have been attached to soil grains in the samples. According to a study by Houba *et al*., (2000), measurement of soil pH and electrical conductivity in 0.01 M solution of calcium chloride is usually better as it will not be affected changes in soil electrolyte and also help to free up more hydrogen ions.

Comparing cation exchange capacity and the total organic carbon percent, samples from Isolo residential area close to the community's water bore hole and Isolo canal sediment have higher amount of CEC and TOC % than the samples from Agbara residential area and Ologe lagoon sediment located in Agbara. This could be because of increase fertility of the Isolo soil probably because of organic waste discharged to the area.

The Results of Drug Standards and their Chromatograms

The results of the standards used are shown below together with their chromatogram for each drug. The HPLC-UV technique (C18, 2.1 x 180 mm, 3.5 um) was used to separate and quantify the standards of pharmaceuticals studied. The chromatograms of the standards are given in the figure 4.1 and 4.2 for 25 ppm and 50 ppm (µg/g) respectively.

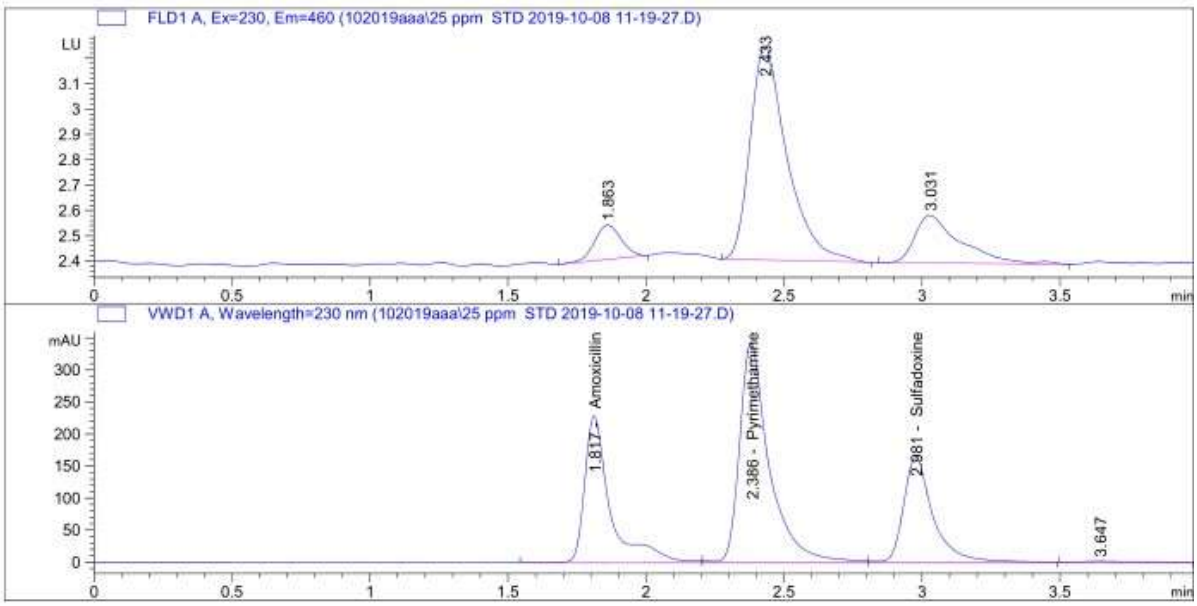

Figure 4.1: The Chromatogram of 25 ppm of analytical standards (Amoxillin, Pyrimethamine, Sulfadoxine).

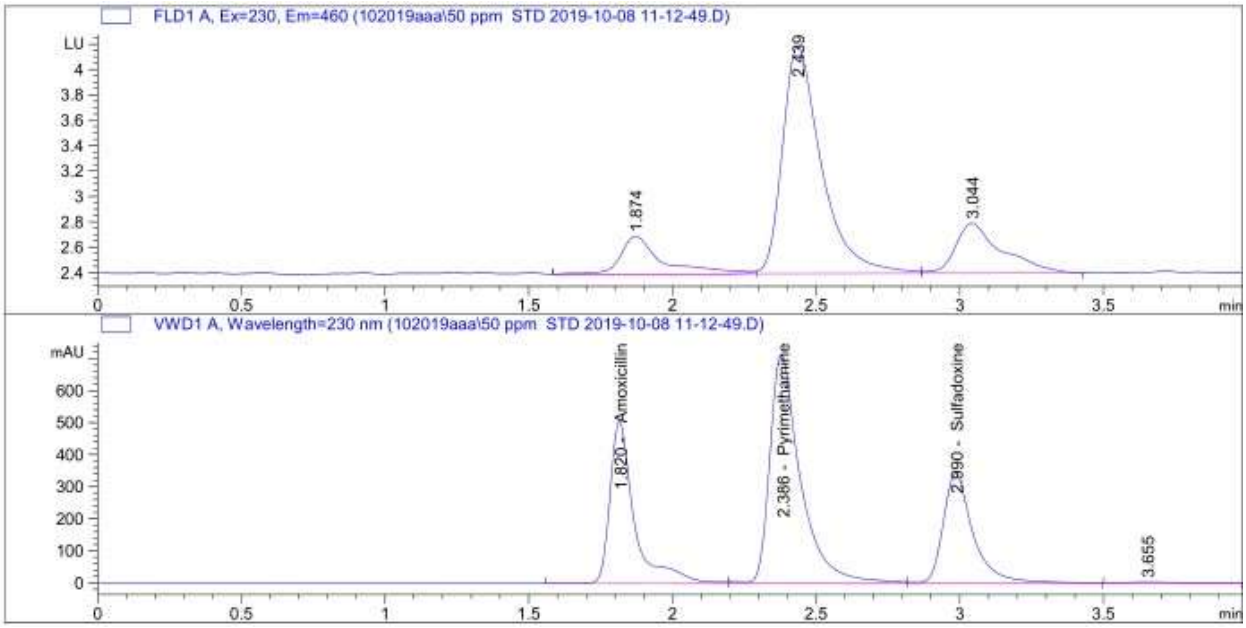

Figure 4.2: The Chromatogram of 50 ppm of analytical standards (Amoxillin, Pyrimethamine, Sulfadoxine)

In the figure 4.1 and 4.2, sulfadoxine has the highest retention time .The chromatograms above were used as standards in determining the concentration of analyte (PHACs) in all the samples by comparing their peak area. Basically, the fundamental of HPLC instrumentation is that peak area in relation to retention time varies directly to the analyte comcentration. The uses of external standards were chosen to cancel out any existing systemic errors of the HPLC-UV detector instrument. Sulfadoxine was eluted at last as it is more polar compound with high solubility which increased its interactions with the stationary phase of HPLC using a mixture of 60% phosphate buffer solution and acetonitrile as mobile phase .The principle used to determine analyte concentration= (Peak area of standard/ peak area of analyte) = (Standard concentration/ analyte concentration). The concentrations and peak areas of the two standard concentrations (25 and 50 ppm) are contained in the appendix.

4.3 Analytical Result and Discussion of Real Samples

The HPLC–UV detector instrument was used to determine the concentration of target pharmaceutically active compounds present in soil of Agbara and Isolo residential areas and sediment of Ologe lagoon and Isolo Canal. At pH 3.0, HLB cartridges were chosen due to its versatility and an improved recovery when extracts from soil and sediment were analysed as observed by Ternes (2003), the table 4.4 contains the concentrations of detected target drugs including Amoxilin, sulfadoxin and pyremetamine. All concentrations of analytes were recorded in parts per million units (µg/g).

Table 4.4: Concentrations of investigated pharmaceuticals in soil from Agbara and Isolo residential areas and Sediment of Ogun River and Isolo canal

Sampling event	Sample codes	Target Analytes	Analyte concentrations (ppm)
1		Amoxicillin	BDL
	OLS1	Pyremetamine	BDL
		Sulfadoxine	BDL
		Amoxillin	BDL
	ARS1	Pyremetamine	0.073 µg/g
		Sulfadoxine	BDL
		Amoxicillin	BDL
	ICS1	Pyremethamine	BDL
		Sulfadoxine	BDL
		Amoxicillin	BDL
	IBS1	Pyremethamine	BDL
		Sulfadoxine	0.17 µg/g
2		Amoxicillin	BDL
	OLS2	Pyremethamine	BDL
		Sulfadoxine	0.15 µg/g
		Amoxicillin	BDL
	ARS2	Pyremethamine	BDL
		Sulfadoxine	BDL
		Amoxicillin	BDL
	ICS2	Pyremethamine	BDL
		Sulfadoxine	0.21 µg/g
		Amoxicillin	BDL
	IBS2	Pyremethamine	0.069 µg/g
		Sulfadoxine	BDL
3		Amoxicillin	BDL
	OLS3	Pyremethamine	0.32 µg/g
		Sulfadoxine	1.13 µg/g
		Amoxicillin	BDL
	ARS3	Pyremethamine	BDOL
		Sulfadoxine	0.16 µg/g
		Amoxicillin	BDL
	ICS3	Pyrethamine	0.27 µg/g
		Sulfadoxine	BDL

		Amoxicillin	BDL
	IBS3	Pyrethamine	BDL
		Sulfadoxine	BDL

In order to study the effects of increase of TOC % on amount of pharmaceuticals in the soil, the average of these parameters are given 4:5:

Table 4.5: Average batches concentrations of analytes and the TOC %, and their correlation coefficient R

Sample code	**Amoxicillin (Average of 3 sampling concentration in ppm)**	**Pyremethamine (Average of 3 sampling concentration in ppm)**	**Sulfadoxine (Average of 3 sampling concentration in ppm)**	**Average TOC %**
OLS	0.00	0.107	0.427	0.985
ARS	0.00	0.0.0243	0.0533	1.8567
ICS	0.00	0.090	0.070	2.256
IBS	0.00	0.0230	0.0567	3.860
Correlation coefficient b/w analyte &%TOC	N/A	-0.66277	-0.69818	1

The bar chart of the average pharmaceutical concentrations of all the batches are drawn below where the bars represent the concentrations and sampling site codes are on the horizontal (X) axis.

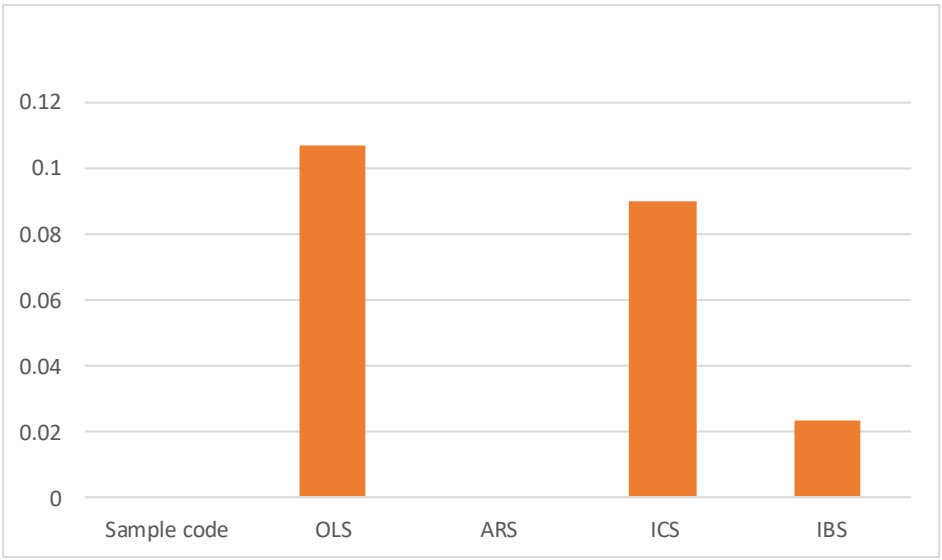

Figure 4.3: Bar chart of average pyrimethamine concentration of the sampling sites

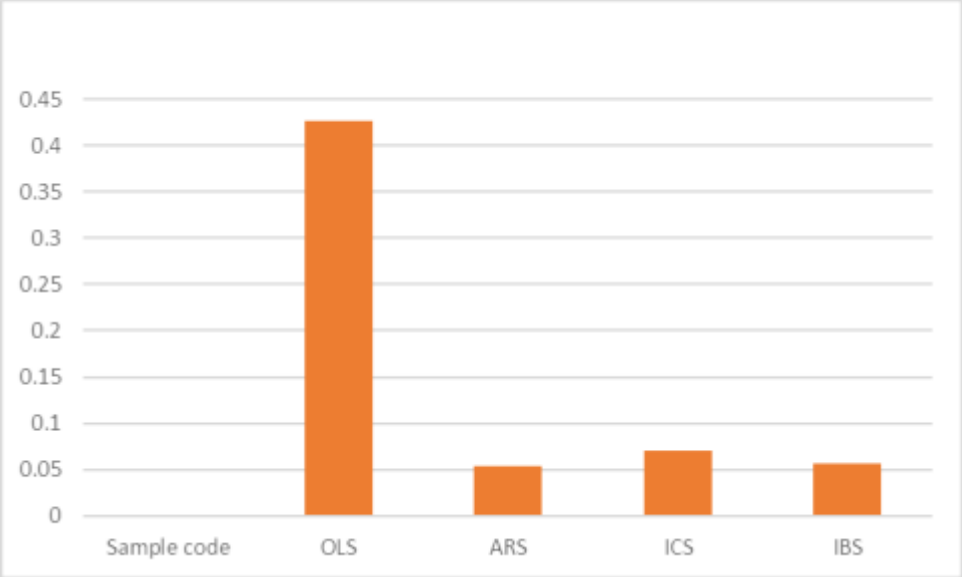

Figure 4.4: Bar chart of average sulfadoxine concentrations of the sampling sites

In this study, pyremethamine and sulfadoxine are detected in many of the samples as could be seen in table 4.4. From figure 4.3 and 4.4, the Lagos ways, Ologe Lagoon and Isolo Canal indicated larger amount of pyrimethamine and sulfadoxine when compared to their concentration in residential areas studied. The average concentration of the two detected PhACs in Ologe lagoon where above the concentrations detected elsewhere (Bjorberg and Elestrom, 2016). The result of this study showed that, Ologe lagoon is polluted with sulfadoxine, having concentration of 1130 ng/g during third sampling. In Ologe Lagoon sediment, contamination of the lagoon by sulfadoxine could be attributed to the discharge of pharmaceutical industrial waste into the river after treatment. There are about three pharmaceutical industries located at Agbara Opic estate close to the river. From the figure 4.1, the Ologe lagoon sediment also contain high amount of pyremethamine when compare to the drugs amount in Agbara residential area soil (ARS), which could be attributed to antimalarial drugs produced by pharmaceutical manufacturing companies located at the estate. As shown in 3.3, sulfadoxine and pyremethamine are among the drugs manufactured by pharmaceutical companies located close to the sites thesamples were collected. Therefore presence of the two antimalarial drugs at higher concentration than detected elsewhere (Bjorberg and Elestrom, 2016) could be because of activities of pharmaceutical companies such as involuntary discharge of waste water into Isolo Canal and Ologe Lagoon.

The prevalence of both pyrimethamine and sulfadoxine drugs were also reported elsewhere because of their common use in rural area for treatment of malaria (Bjorberg and Elestrom, 2016).The human use of antimalarial drugs (pyrimethamine and sulfadoxine), as malaria is the most common illness in tropical area like Agbara, also contributed to the high concentrations of these drugs in the environment studied , as could be justified by the presence of these drugs in Agbara residential area soil (ARS) close to water bore hole at the community. According to

Bjorberg and Elestrom, (2016), Malaria is the common illness in tropical Africa countries. In a recent study by Ternes, (1998), conjugated compounds during STP or WWTP operation have been shown to easily de-conjugate which ultimately increase the concentration of analyte in the effluent than the influent. Therefore, even though waste water discharged into the Ologe Lagoon could have been treated, the amount of antimalarial drugs, which the pharmaceutical companies located at Agbara axis, produced were higher in Ologe Lagoon sediment compare to other sampling sites. The treatment of waste water at the Estate has little or no effect on sulfadoxine and pyrimethamine drugs.

Comparing the amount of pharmaceuticals detected in the samples with respect to the total organic carbon of the sample, there is inverse relationship between two parameters as showed in their correlation coefficients. According to a study by Castiligioni *et al*. (2006), the WWTP removal of amoxicillin was observed to be 75-100 % , therefore the sewage and any industrial waste water may have been treated before they were probably discharged into Ologe lagoon or Isolo canal which consequently removed all the amoxicillin in the two study areas. Therefore, all the samples analysed indicated the amount of amoxicillin below detection limit (BDL)s. Sulfadoxine was prevalent in all the samples from rural area which include Agbara residential area and sampling point at Isolo residential area close the water bore hole at Isolo community, which are densely populated areas. The amount of pyrimethamine detected at OLS3 (Ologe Lagoon Sediment of third sampling event) is higher than the amount detected elsewhere (Bjorberg and Elestrom, 2016). This could be because of existence of many pharmaceutical industries located at Opic estate Agbara, which discharge their treated waste directly into the river. The pyrimethamine and sulfadoxine are very stable chemical compounds in acidic environment according to recent study by Ngobiri et al., (2017) , which could be cause of them being detected in many of the samples.

Table 4.6: Correlation coefficients of all physic-chemical parameters with TOC %

Batch	**1**	**2**	**3**
Correlation coefficient R Between average TOC % And CEC	**0.8356**	**O.9369**	**0.96891**
TOC % Correlation with soil conductivity	0.327002	**0.80207**	**-0.30018**
TOC % Correlation with soil pH	**-0.89474**	**-0.94032**	**-0.00642**
TOC % Correlation with Soil CEC	**0.83565**	**0.936982**	**0.96899**

There is a good correlation between cation exchange capacity and %total organic carbon in all the samples with R >0.8 as showed in table 4.6. The higher the % of total organic carbon, the higher the cation exchange capacity. Therefore increasing organic carbon such as adding manure or humus to the soil increases the amount of cation exchange capacity.

From the Table 4.5, the increase in amount of pharmaceuticals in all studied sites gave negative correlation coefficient by increase in amount of total organic carbon, which were proportional to decrease of target pharmaceuticals in studied areas. This could be due to the soil ion suppression effects as observed by Magner *et al.*, (2016).

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CONCLUSION AND RECOMMENDATION

Conclusion

In this study, antimalaria drugs were the analytes detected in all the samples. All the samples collected in residential areas with a high dense population indicated considerable presence of pyremethamine and sulfadoxine with Isolo borehole area soil (IBS) having 0.069 µg/g and 0.17 µg/g for pyrimethamine and sulfadoxine respectively and ARS having 0.073 µg/g and 0.16 µg/g for pyrimethamine and sulfadoxine respectively. Ologe Lagoon sediment has higher concentration of sulfadoxine of 1.13 µg/g compare to Isolo Canal sediment with sulfadoxine of 0.21 µg/g.

The results of this investigation indicated that Ologe Lagoon sediment (OLS) sample has the highest amount of sulfadoxine, even though dredging activity was steady where the sample was collected. Comparing OLS average sulfadoxine to the amount detected in Agbara residential area soil (ARS), discharge of treated Agbara industrial Estate waste water into the river could be the source of high amount of the drug in the river which ultimately would settle down in the bottom of the river (sediment).

Presence of these antimalaria drugs at ppm level in environment, which may be due to prevalence of malaria at both studied sites, could lead to increase resistance to drugs by malaria causing pathogens (Guardabasi *et al*., 1998). The stability of pyrimethamine and sulfadoxine in the soil could be cause of them being detected in most of the samples (Ngobiri et al., 2017) .

The cation ion exchange capacity and total organic carbon percent of the OLS were lowest compare to others , which indicated that increase in amount of pharmaceuticals (sulfadoxine and pyrimethamine) were negatively correlated to the physico-chemical parameters of the sampling site. Amoxicilin was not detected in all the samples probably because of its lower half life in the soil and its high removal percent of 75-100% in waste water treatment plant (WWTP) as stated by Castiglioni *et al,* (2006). In all samples, increase in TOC % leads to increase in cation exchange capacity (CEC) of top soil as shown in Table 4.5 correlation coefficient.

RECOMMENDATION

Considering the impediment of drug resistance by pathogenic micro- organism, more researches are needed for detection and quantification of amoxicillin and other pharmaceuticals in order to generate a baseline data for all pharmaceuticals prone to induce drug resistance in micro-organism due to their presence in environment.

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