Fate and removal of emerging contaminants during chlorination in drinking water

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ABSTRACT

The prevalence of emerging contaminants (ECs) in drinking water is among the emerging challenges for the water industry. The problem is more complex in the developing world, where the water and sanitation facilities are underdeveloped, and the consumption of pharmaceuticals is relatively higher due to fewer healthcare facilities. Consequently, the occurrence of ECs in surface water is well reported in the literature. The presence of ECs in surface water therefore makes it necessary to investigate their removal in conventional drinking water treatment plants (DWTPs). A class of ECs known as antiretrovirals (ARVs) is commonly consumed on the African continent due to the prevalence of acquired immunodeficiency syndrome (AIDS). The chlorination process in DWTPs can have some potential for the removal of these ARVs. However, investigations on the interaction between the chlorination process and ARV removal are scarce. Therefore, the objective of this study was to investigate the removal of five ECs from conventional DWTPs. The ECs selected for the investigation were Nevirapine and Efavirenz (antiretroviral drugs), Atenolol (beta blocker), Sulfamethoxazole (antibiotic), and Carbamazepine (antiepileptic drug). Further, the chlorination process was in depth investigated to understand its kinetics, the effects of operational parameters, and the formation of disinfection by-products during the removal of two ARVs (Nevirapine and Efavirenz).

To identify and measure the ECs, Ultra-High-Performance Liquid-Mass Spectrometry (uHPLC-MS) was used. In addition, laboratory studies were conducted to determine the effect of operational parameters on the removal of selected antiretroviral (Nevirapine and Efavirenz) and the formation of disinfection by products during chlorination. During optimization, the solid-phase extraction conditions for all five ECs were achieved at a pH of 3, with an average recovery rate of 64% between all selected ECs. In ascending order, the average EC concentrations detected from the influents were: Sulfamethoxazole (114.37 ng/L), Carbamazepine (118.69 ng/L), Efavirenz (156.12 ng/L), Nevirapine (164.06 ng/L), and Atenolol (197.47 ng/L), respectively. Atenolol exhibited the highest concentration levels among all the ECs in the influent.

Nevirapine however demonstrated the highest risk quotient (RQmax) values after post-chlorination, particularly in toddlers. The treated effluent showed a significant reduction in the amount of EC detected which was below detection and quantification level. The average removal efficiencies of ECs between the raw influent to the treated effluent where as follows: Sulfamethoxazole (87.17%), Nevirapine (85.32%), Carbamazepine (79.94%), Atenolol (76.99%), and Efavirenz (70.89%). Notably, Sulfamethoxazole exhibited significantly higher degradation and removal rates in all three DWTPs compared to the other four ECs. Using laboratory (batch) experiments, the second phase of the study examined the interaction of Nevirapine and Efavirenz with chlorination process with a prime focus on the effect of operational parameters (pH, temperature, chlorine dosage and compound concentration) and kinetics. The maximum removal of Nevirapine (97%) and Efavirenz (90%), was observed at pH=7.5 and temperature 25ºC and chlorine concentration of 3 mg/L. It was further observed that Efavirenz was removed better at basic pH than acidic (37% removal at pH 5.5 versus 68% at pH 8). A threefold increase in temperature from 10ºC to 30ºC increased the removal of Nevirapine by 42% and Efavirenz by 39%. Higher chlorine dosages of 3 mg/L and 5 mg/L showed efficient removal of both compounds (90 - 97%). The maximum values of pseudo second order rate constant (K_{app}) of Nevirapine and Efavirenz were 109.67 x $10^{-2} M^{-1}. s^{-1}$ and 95.47 x 10^{-2} $M^{-1}. s^{-1}$ at optimum conditions. The estimated the hydraulic residence time (HRT) for both ARVs was within the practical limits of 1-2 hours, considering a continuous stirred-tank reactor configuration and a chlorine dose of 2 mg/L.

Further, the study investigated the formation of disinfection by-products (DBPs), specifically trihalomethanes (THMs), namely chloroform ($CHCl_3$), dibromochloromethane ($CHBr_2Cl$), and bromoform ($CHBr_3$), during chlorination of the two ARVs (Nevirapine and Efavirenz). Notably, among the two drugs, Efavirenz degradation produced the highest formation of THM observed in $CHCl_3$ (63.49 µg/L) followed by $CHBr_2Cl$, (25.83 µg/L) and $CHBr_3$ (11.94 µg/L). This occurred under specific conditions, including a temperature of 25 ºC, a reaction time of 6 hours, a pH of 7.5, and a residual chlorine concentration of 0.1429 µM. Furthermore, the study revealed interesting insights into the kinetics of trihalomethane formation. The highest rate K_{app} for trihalomethanes was observed in $CHBr_2Cl$, with a remarkable value of 7.722 x 10^{-4} $M^{-1} \cdot s^{-1}$, under the following conditions:100 µg/L efavirenz, at 25°C, chlorine concentration of 0.1426 µM, and a pH of 7.5.

Conversely, the lowest K_{app} value for trihalomethanes was found for $CHBr_3$, which exhibited a K_{app} value of 9.33×10^{-4} $M^{-1} \cdot s^{-1}$ under the same conditions. Importantly, the investigation discovered that the K_{app} for $CHCl_3$ and $CHBr_2Cl$ formation during the degradation of Efavirenz were higher compared to those observed during the degradation of Nevirapine.

This research study addressed the knowledge gap regarding EC pollution in South African drinking water by conducting a risk assessment and investigating the occurrence and removal efficiencies of specific ECs in DWTPs in KwaZulu-Natal, South Africa. The findings highlight the need for tailored approaches considering the specific characteristics and sources of ECs in the country, as complete adoption of EC management practices from developed countries may only partially mitigate EC pollution in South Africa. There is also a vital need to investigate the DPBs in an up-scale environment to assess the prevalence of DBPs in different water matrices.

DECLARATION BY STUDENT

I declare that this thesis, submitted for Doctor of Philosophy in Chemistry at the Durban University of Technology, is the original work of the author and has not been submitted for a degree at any other University. Where use is made of any author's work, it has been duly acknowledged.

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I hereby approve the final submission of the following thesis.

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CONFERENCES AND PUBLICATIONS

Oral presentation: 2nd Canadian IWA Young Water Professionals, 1-2 June 2023, International conference, Vancouver BC, Canada. *Exploring Chlorination as a Removal Process for Antiretroviral Drugs (Nevirapine and Efavirenz) from Water: Effect of Operational Parameters, Kinetics, and Trihalomethane Formation*

Khalid Muzamil Gani, Hlongwa, Nhlanhla, Taher Abunama, Sheena Kumari Kuttan, Faizal Bux, Emerging contaminants in South African water environment- a critical review of their occurrence, sources, and eco-toxicological risks

Nhlanhla Hlongwa, Khalid Muzamil Gani, Sheena Kumari Kuttan, Kriveshin Pillay, Faizal Bux, Exploring Chlorination as a Removal Process for Antiretroviral Drugs (Nevirapine and Efavirenz) from Water: Effect of Operational Parameters, Kinetics, and Trihalomethane Formation

Nhlanhla Hlongwa, Khalid Muzamil Gani, Sheena Kumari Kuttan, Faizal Bux,

Surveillance of Emerging Contaminants of Concern and Their Toxicological Risks in KwaZulu-Natal Drinking Water

DEDICATION

My work is a tribute to my family and dear loved ones. To my grandma, uGogo Gugu Innocentia Hlongwa, in particular, for her insightful advice and words of support.

Being confident of this, that He who began a good work in you will carry it on to completion until the day of Christ Jesus.

Philippians 1:6

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LIST OF ABBREVIATIONS

µg/L	Micrograms per liter
mg/L	Milligrams per liter
ng/L	Nanograms per liter
NVP	Nevirapine
CBZ	Carbamazepine
EFV	Efavirenz
ATN	Atenolol
SMXZ	Sulfamethoxazole
Cl_2	Chlorine
K_{app}	Apparent 2nd constant rate kinetics
WWTP	Wastewater treatment plant
DWTP	Drinking water treatment plant
ECs	Emerging contaminants
pKa	Dissociate constant
DPBs	Disinfection by-product
THMs	Trihalomethane
TTHMs	Total Trihalomethane
LC-MS	Liquid chromatography-Mass spectrometry
GC-MS	Gas chromatography-Mass spectrometry
SPE	Solid phase extraction
SPME	Solid phase micro-extraction
DCM	dichloromethane
TCM	chloroform
CDBM	dibromochloromethane
$CHBr_3$	bromoform
ARVs	Antiretroviral drugs
FA	Formic acid
HIV	Human immunodeficiency virus

Chapter 1: Introduction

1.1 Introduction

Emerging contaminants (ECs) in wastewater, surface water, and drinking water are a global concern. The Environmental Protection Agency (EPA) in the United States has identified over 600 ECs in drinking water sources, including insecticides, pharmaceuticals, and industrial chemicals (Gomes *et al.*, 2020). Similar findings have been reported in European drinking water sources, such as perfluorinated chemicals and microplastics (MP) (Schymanski *et al*., 2014; Jiang *et al*., 2017; Lee *et al*., 2018). The ECs pose significant risks to human well-being, such as disrupting the endocrine system and leading to imbalances in hormone levels (Gomes *et al*., 2020). Several organic pollutants and heavy metals have been linked to various health problems, while prolonged exposure to low concentrations of antibiotics can lead to antibiotic resistance (Morin-Crini *et al*., 2021; Parida *et al*., 2021). Additionally, ecological disturbances caused by ECs can indirectly impact human health by disrupting natural equilibrium and potentially affecting food resources (UNESCO, 2021). Aquatic environments globally, including those in South Africa (SA), are affected by various types of ECs (Gani et al., 2021). Furthermore, plastic debris, household and consumer products, and the unintentional discharge of crude oil or petroleum products contribute to pollution (Abafe et al., 2023). Inadequate treatment of wastewater can result in the discharge of these drugs into freshwater bodies, which serve as sources for drinking water treatment plants (Abafe et al., 2023). In SA, wastewater treatment plants are the primary source of ECs (Gani et al., 2021). SA exhibits a notable incidence of individuals with compromised immune systems owing to the high prevalence of acquired immunodeficiency syndrome (AIDS) and the human immunodeficiency virus (HIV). According to Claasens *et al.* (2020), the nation is recognized for harbouring the most significant HIV-seropositive populace worldwide, comprising 7.2 million individuals who are living with HIV. Moreover, it has been reported that around 20% of fresh HIV infections transpire in SA (De Cock and Weiss, 2000). SA is also recognized for its elevated prevalence of high blood pressure health conditions, tuberculosis (TB), and diverse bacterial infections, as reported by Gani *et al.* (2021) and Sambandamurthy *et al.* (2006).

As a result, SA is among the countries facing the issue of drinking water contamination with ECs, which include antiretroviral drugs, antibiotics, and personal care products. Which pose a significant concern for water quality and public health in the region. It is worth noting that Sub-Saharan Africa has a relatively low frequency of antibiotic administration, with a median national usage rate of 43% (Maina et al., 2016). However, only a certain percentage of these drugs are metabolized in the body, and the remainder is discharged into the environment in their original form (Daughton and Ruhoy, 2009). Some of these ECs can persist in the environment for an extended period (Gomez and McKinney, 2004). Westerhoff *et al.* (2005), reported that drinking water coagulation treatment units in the United States of America (USA) exhibited less than 25% removal efficacies for ECs and endocrine disruptor compounds. In Michigan, various ECs showed removal efficiencies ranging from 85% to 99% in reverse osmosis and membrane filtration treatments. Furthermore, in Colombia, Brazil, and Brazil (Rio Grande), ibuprofen, caffeine, atrazine, and bisphenol A were found with concentrations ranging from 7 to 18,828 ng/L (Aristizabal-Ciro *et al*., 2017, Machado *et al.,* 2016, Caldas *et al.,* 2019, Peña-Guzmán *et al.,* 2019). Additionally, in South Europe regions, water treatment plants exhibited ECs removal efficiency of only 7% when using flocculation with rapid sand filtration (Peña-Guzmán *et al.,* 2019). Lastly, disinfectants employed in nine provinces of SA showed EC removal efficacies ranging from 14% to 69% (Momba *et al.,* 2009). Including various treatment units, such as rapid gravity filtration, pressure filters, and slow sand filtration systems, accounted for removal efficacies ranging from 9% to 60% (Momba *et al.,* 2009). The effectiveness of treatment units can vary depending on the nature of the ECs and the specific treatment methods employed. The general treatment configuration involves multiple stages to purify and enhance the quality of the water supply. The raw water is initially treated through screening and sedimentation, followed by coagulants and tertiary treatment with sand filtration, granular activated carbon filtration, and advanced oxidation (O'Melia 1998; Rosińska and Dąbrowska 2021; Li *et al.* 2022; Foundation 2023). Subsequently, the process of chlorine disinfection is commonly employed in water treatment plants, both as pre-chlorination before raw water moves to coagulation and as post-chlorination at the final stage of the treatment process (Potgieter 2019; Jalali Milani and Nabi Bidhendi 2022). Chlorination is the most used disinfection method globally in both drinking water and wastewater treatment plants. The method involves introduction of chlorine in various forms, such as elemental chlorine gas or sodium hypochlorite solution (Ahmed *et al.* 2021).

The interaction between chlorination and EC removal dynamics encompasses various reactions, including oxidation-reduction (REDOX), addition, and substitution reactions. It depends on factors such as the compound's nature and treatment conditions. Chlorinated compounds, including ECs, undergo reductive pathways due to chlorine's electronegativity, involving chlorine atom reduction (Rodrigues *et al*., 2020). EC removal may also alter the oxidation-reduction potential (ORP), indicating REDOX reactions (Kirkpatrick, 2011). Oxychlorination processes introduce complexity, leading to various routes like substitution, addition, elimination, and oxidation (Ma *et al.,* 2020).

A chlorine dosage of 1 mg/L effectively degrades indomethacin and propyphenazone within 30 minutes, resulting in complete degradation (Simazaki *et al.,* 2008). However, naproxen and diclofenac show approximately 70% removal after 24 hours (Simazaki *et al.,* 2008). Additionally, ibuprofen, ketoprofen, fenoprofen, gemfibrozil, and clofibric acid exhibit 80% removal within 24 hours (Simazaki *et al.,* 2008). The use of chlorination presents a drawback in the form of the creation of disinfection by-products (DBPs). These DBPs, including trihalomethanes (THMs) and haloacetic acids (HAAs), pose a significant risk to human health, even at low concentrations, and have the potential to accumulate in the body (Lee *et al*., 2013; Vizioli, Hantao, & Montagner, 2022). In the context of water sources, ECs such as pharmaceuticals and pesticides, which fall under the category of organic compounds, can act as precursors for the generation of DBPs during the chlorination process (Bulman and Remucal, 2020). Notably, the presence of chlorine at concentrations exceeding 1 mg/L resulted in a notable increase in the formation of chloral hydrate, THMs, and trihaloacetonitriles (Lee and Lee, 2015). Varying the chlorine dosage at levels of 1, 3, 5, and 7 mg/L yielded corresponding concentrations of THMs of 31.71, 33.23, 35.73, and 36.77 μg/L, respectively (Niu *et al.,* 2017). Monitoring these ECs and their disinfection byproducts in the environment however is limited by equipment availability and detection methods. The currently available analytical instrumentation, such as liquid and gas chromatography mass spectrometers, has limitations in detecting ECs, as they are only capable of detecting concentrations at the milligrams per liter (mg/L) level and primarily focus on the parent ion of the ECs (Kaklamanos *et al.* 2020). In contrast, high-tech analytical instruments like ultra-high liquid chromatography-mass spectrometry (uHPLC-MS), gas chromatography-mass spectrometry (GC-MS), high-resolution mass spectrometry (HRMS), inductively Coupled Plasma-Mass Spectrometry (ICP-MS), Ion Chromatography (IC), and time-of-flight mass spectrometry (TOF-MS), have the capability to detect ECs at trace levels as low as nanograms per liter (ng/L) (Karasek and Clement 2012).

Furthermore, these advanced instruments can identify multiple fragmentation products of each EC, enhancing the overall analysis and understanding of their presence.

1.2 Research problem

In SA, a continuous presence of antiretroviral drugs (ARV), beta-blocker drugs, epileptic drugs, and various other pharmaceutical compounds have been reported from various aquatic environments (Ngqwala and Muchesa, 2020). This occurrence is primarily attributed to the significant prevalence of AIDS, HIV infections (Abafe *et al.* 2018), anti-epileptic conditions (Jacobs *et al.* 2016), and elevated blood pressure complications within the country (Duncan *et al.* 2014). Occurrence levels of certain ECs have been reported in different regions of South Africa. Specifically, Nevirapine and Efavirenz were detected at levels of 13 ng/L in the Hartbeespoort dam catchment and 354 ng/L in the Juskei River. Additionally, atenolol was found at a level of 31,000 ng/L, while sulfamethoxazole was detected at a level of 2300000 ng/L, these measurements were obtained from households near eThekwini (Gani et al., 2021). Additionally, surface water is the primary raw water source for drinking water treatment plants in the country (Kawamura 2000). The extent of their presence in different drinking water treatment plants and their removal during the treatment process are, however, poorly documented. Consequently, it is critical to understand their levels in different drinking water treatment plants and the effectiveness of treatment processes for their removal. This includes their influence on disinfection byproduct formation during chlorination. This knowledge is essential for assessing the risks associated with these compounds, ensuring that drinking water is safe, and setting regulations to protect public health (Gilca *et al*. 2020; Li *et al*. 2020; Pivokonský *et al.* 2020).

1.3 Research Aim

To investigate the occurrence of selected ECs in KwaZulu Natal drinking water treatment plants and to assess the effect of operational parameters on ECs removal during chlorination.

Objective 1: To determine the occurrence level of selected emerging contaminants in source water and effluent of selected water treatment plants.

Objective 2: To determine the removal efficiencies of selected ECs at different treatment units of the selected drinking water treatment plants.

Objective 3: To determine the effect of operational parameters viz., initial chlorine concentration, pH, initial EC concentration and temperature during the removal of ECs by chlorination process.

Objective 4: To analyse the formation of disinfection by products (DBPs), specifically trihalomethane (THMs) during the degradation of ECs by chlorination.

1.4 Thesis framework

The framework for this thesis is presented in the graphical depiction below.

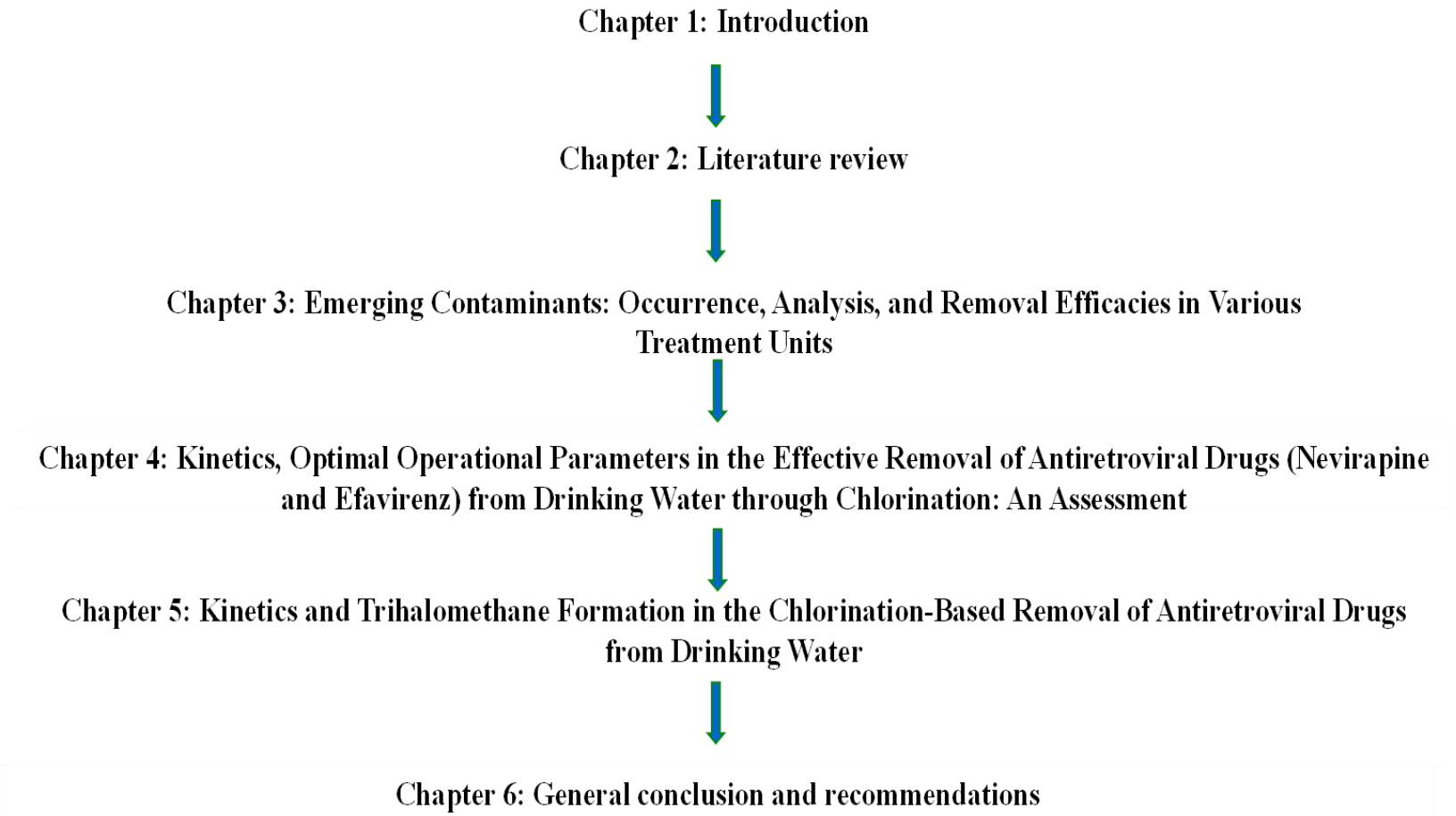


Figure 1: Thesis framework

Chapter 2: Literature review

The following sections in this chapter have already been published (2.1-2.6.3 and 2.8) in the Journal of Chemosphere: *Gani, K. M., Hlongwa, N., Abunama, T., Kumari, S. and Bux, F. 2021. Emerging contaminants in South African water environment- a critical review of their occurrence, sources, and eco-toxicological risks. Chemosphere, 269: 128737*. (Front page, Appendix 1)

2.1 Literature review

Emerging contaminants (ECs) are widely distributed in the environment, which include a broad range of natural and chemical compounds, such as pharmaceuticals, hormones, personal care products, phthalates, and surfactants. The advances in analytical techniques and instrumentation have enabled researchers to detect a broad spectrum of ECs which are present at low concentrations in aquatic sources such as drinking water, groundwater, surface water, and wastewater (Abafe *et al*., 2018; Godfrey *et al.,* 2007; Swartz et al., 2006;). Due to their potential toxicity and negative impact on the ecosystem and human health, abatement of ECs in the aquatic environment has attracted the attention of the World Health Organisation (WHO) (Schriks et al., 2010). Wastewater reclamation has a vital role in the augmentation of water supply in the water-stressed African continent. Only 22-34 per cent of the population in eight sub-Saharan countries have access to safe water and projections are that roughly half of the African continent will face severe water scarcity by 2025 (Tatlock, 2006). Lack of infrastructure, rapidly growing urban areas, insufficient scientific research, and mismanagement of resources have aggravated the problem of water stress in the region. In South Africa, wastewater reclamation has been identified as one of the vital approaches in the South African National Water Resource Strategy, to achieve the delicate balance between water availability and demand (Kemp, 2017). However, if the wastewater treatment is not effective for the removal of ECs, it can pose serious health risks in humans, when used for portable purposes. Existing wastewater treatment technologies are not designed for efficient EC removal; hence such compounds could easily find their route to the receiving aquatic environment (Swartz *et al.,* 2018).

In European countries, legislative and regulatory efforts such as the Water Framework Directive (WFD) have been laid out to protect or reduce pollution of ECs in aquatic sources (EC, 2000; 2006; 2008). The primary aim of WFD is to establish a priority list of ECs for the regular monitoring of water sources. Similarly, the Canadian government has increased support for institutional and academic research on ECs in the water environment, which is further advanced through various international cooperation programmes. This included the development of a national gazette containing proposed discharge regulations of several ECs in wastewater effluents (Environment Canada, 2011). Different authors (Gani *et al*., 2016; Philip *et al.*, 2018; Stuart *et al*., 2012; Zhou *et al.*, 2019) globally have extensively reviewed the regional distribution of ECs in different environmental matrices. These reports could act as a framework to identify the deficiencies in the global data and to set out future research primacies. However, published literature reviews regarding the occurrence and distribution of ECs in the water environment are not available from South Africa, which is the most developed country in Africa. Therefore, the main objective of this review is to consolidate the available data on the occurrence and major sources of ECs in the water environment of South Africa. The data compiled is used as a baseline to establish the level of contamination and prioritize ECs in different water matrices so that ECs present in unexpectedly higher concentrations can be gauged in future monitoring plans. In addition, a risk assessment of the reported ECs is performed to augment the understanding of the risks associated with their presence in the aquatic environment. Figure 2 below illustrates a summative depiction of the sources and fate of ECs.

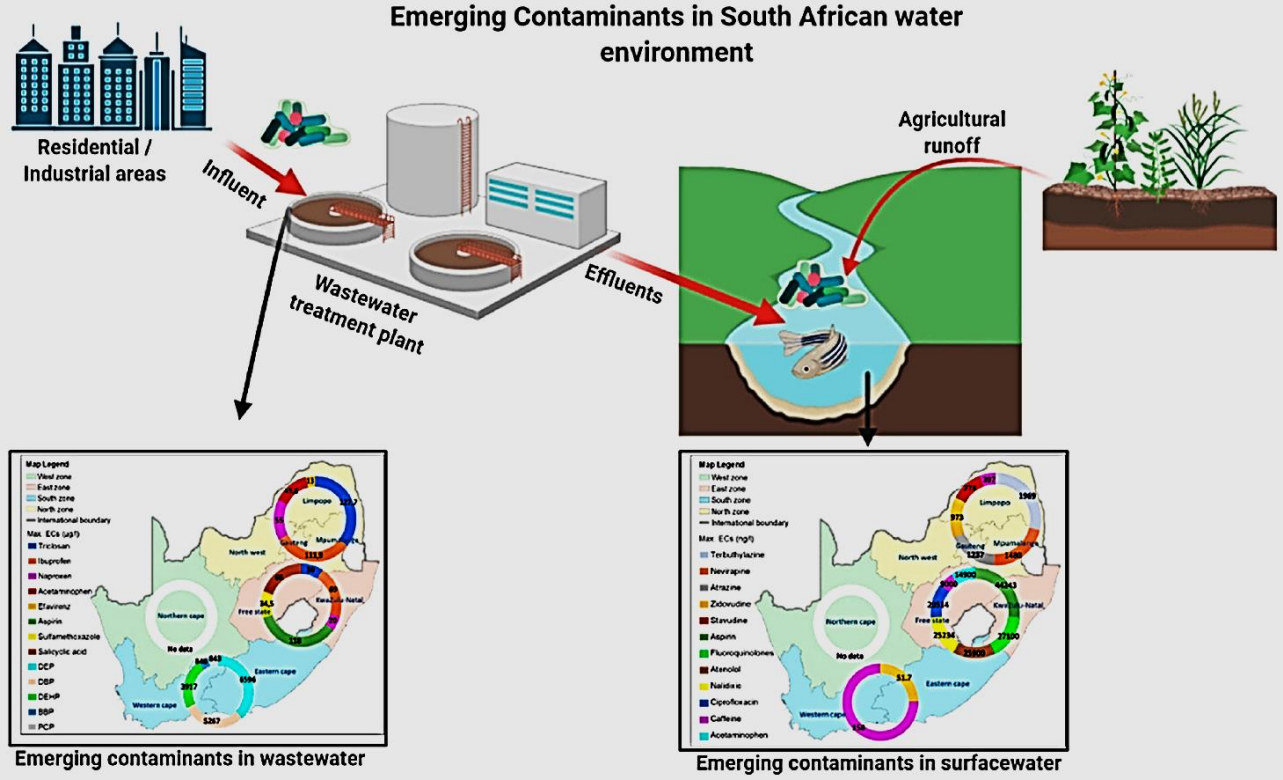


Figure 2: A summative depiction of the sources and fate of ECs

2.1.1 Review method

This review was prepared based on the literature sought from various databases such as Web of Science, Scopus, Google Scholar, etc. using the keywords "emerging contaminants –water-South Africa" OR "micro pollutants-water-South Africa" OR "pharmaceuticals-water-South Africa". The primary set of literature was then grouped into four main geographical zones (north, south, east, and west), based on the study area (Figure 3). The provinces distributed among the four identified geographical zones are the North zone (Limpopo, Mpumalanga, Gauteng, and Northwest), South zone (Eastern Cape, Western Cape), East zone (Kwazulu-Natal, Free State) and West zone (Northern Cape). The literature published from indexed journals from 01 Jan 2000 - 30 April 2020 has been included in this review. The broad categories of emerging contaminants considered for this review are endocrine-disrupting chemicals, pharmaceuticals, industrial chemicals, personal care products and pesticides. The terms used for different water matrixes in this review were freshwater, drinking water, and surface water with their respective domain assumed as freshwater (drinking water and surface water); drinking water (the effluent of drinking water treatment plant (DWTP), tap water and groundwater), surface water (rivers, lakes, dams, oceans, and influent of DWTP). The removal of ECs in wastewater treatment plants (WWTPs) was calculated from the reported influent and effluent concentrations in literature. The removal performance discussed in this review is overall removal (primary, secondary, and tertiary) of a compound in WWTPs.

2.1.2 Overview of research related to ECs in South African water environment.

Based on the literature search, the total number of publications that focused on ECs in the water environment of South Africa from 01 Jan 2000 - 30 April 2020 was 41. The highest number of publications has emanated from the North zone (18), followed by East zone (14) and South zone (9), however, no data was available for the West zone (Figure 3). The ECs reported in drinking water, surface water and wastewater in different zones of South Africa are listed in Table 1. Most publications are based on wastewater (Table 1), indicating that the direction of EC monitoring in the country is more focused on wastewater than surface water and drinking water. The highest number of ECs was reported from wastewater (129), followed by surface water (58) and drinking water (06).

The total number of publications related to ECs in the water environment of South Africa is lower than the European and North American countries. A similar search carried out on the web of science on 30 April 2020, resulted in more than 300 outputs from Germany, Spain and Canada. This lower volume of institutional and academic research outputs in South Africa may be due to the limited infrastructure facilities for EC analysis in South African laboratories (Swartz *et al.*, 2018). Balfour *et al.* (2011) surveyed approximately 100 laboratories to understand the possible reasons for the underrated contribution in EC related research in water bodies and stated that the high costs associated with ISO 17025 accreditation were the primary bottleneck. Swartz *et al.* (2018) proposed that the above challenge could be overcome by establishing a network of laboratory facilities at the national level that can cater to the specialized analysis of water samples.

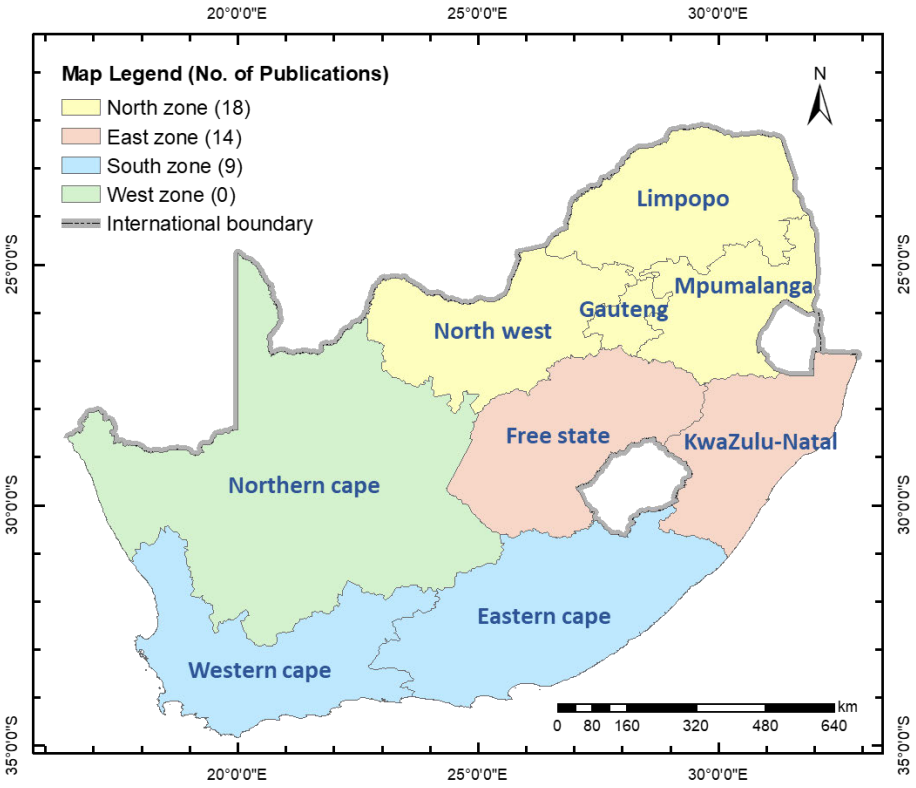


Figure 3: Distribution of South African provinces adopted in this study and ECs related publications from each zone.

Table 1. List of all ECs detected in various water matrices (drinking water, surface water, and wastewater) of South Africa

Matrix	Zone	Maximum concentration (ng/L)	Category	Compound	Reference
Drinking water	North	0.02-220	Pesticides	Atrazine, Terbuthylazine	(Patterton 2013), (Odendaal *et al.* 2015)
			Steroids	Estrone (E1), Estradiol (E2), Ethynyl-oestradiol	(Van Zijl *et al*. 2017)
			Antiretroviral	Zalcitabine, Zidovudine,	(Patterton 2013), (Odendaal *et al.* 2015)
			Anti-epileptic	Carbamazepine	(Patterton 2013), (Odendaal *et al*. 2015)
	South	0.003-10	Pesticides	Atrazine, Terbuthylazine	(Patterton 2013), (Odendaal *et al*. 2015)
			Steroids	Estrone (E1), Estradiol (E2), Ethynyl-oestradiol	(Van Zijl *et al*. 2017)
			Anti-epileptic	Carbamazepine	(Patterton 2013), (Odendaal *et al.* 2015)
	East	10-330	Pesticides	Atrazine, Terbuthylazine,	(Patterton 2013), (Odendaal *et al.* 2015)
			Anti-epileptic	Carbamazepine	(Patterton 2013), (Odendaal *et al.* 2015)

	West			No data	
Surface water	North	0.2-1969	Antiretroviral	Nevirapine, Efavirenz, Lamivudine, Zidovudine, Indinavir, Ritonavir	(Rimayi *et al*. 2018), (Wood *et al.* 2015)
				Zalcitabine, Emtricitabine, Stavudine,	(Rimayi *et al*. 2018), (Wood *et al.* 2015)
				Tenofovir, Didanosine, Abacavir,	(Rimayi *et al.* 2018), (Wood *et al.* 2015)
			Anti-epileptic	Carbamazepine,	(Archer *et al.* 2017)
			Human indicators	Caffeine,	(Wood *et al.* 2015)
			Pesticides	Atrazine, Simazine, Terbuthylazine, Ametryn, Prometon, Gesatamin, Propazine,	(Rimayi *et al.* 2018)
			Alkylphenol ethoxylates	Nonylphenol, Octylphenol pentaethoxylates, Di-nonylphenol ethoxylates (di-NPE1), di-NPE2, mono-NPE, Nitrophenyl Phenyl Ether (NPPE1), NPPE2,	(Chokwe *et al.* 2015)
				Polybrominated biphenyls (PBB101), brominated diphenyl ether (100), brominated diphenyl ether (99), brominated diphenyl ether (154),	(Chokwe *et al.* 2015)

			brominated diphenyl ether (153), brominated diphenyl ether (183) Hexabromocyclododecane,	(Chokwe *et al.* 2015)
		polychlorinated biphenyls	Polychlorinated biphenyl (PCBs), Octacalcium phosphates (OCPs)	(Amdany *et al*. 2014)
		dichlorodiphenyltrichloromethane	Dichlorodiphenyltrichloroethane (DDT)	(Amdany *et al*. 2014)
		Anti-depressants	Fluoxetine,	(Archer *et al.* 2017)
		Diabetes	Gliclazide, Metformin	(Archer *et al.* 2017)
		Antibiotics	Azithromycin, Clarithromycin, Sulfamethoxazole, Sulfasalazine, Trimethoprim	(Archer *et al.* 2017)
		Anti-inflammatory drugs	Acetaminophen, Diclofenac, Ibuprofen, Ketoprofen,	(Archer *et al.* 2017)
South	51.7-158	Antiretroviral	Zalcitabine, Tenofovir, Lamivudine, Didanosine, Stavudine	(Wood *et al.* 2015)
			Zidovudine, Nevirapine, Indinavir, Ritonavir, Abacavir	(Wood *et al.* 2015)
		Human indicators	Caffeine	(Wood *et al.* 2015)
East	28.2-44243	Antiretroviral	Zalcitabine, Tenofovir, Lamivudine, Didanosine, Stavudine	(Wood *et al.* 2015)
			Zidovudine, Nevirapine, Indinavir, Ritonavir, Abacavir,	(Wood *et al.* 2015)

			Anti-inflammatory drugs	Aspirin, diclofenac, Ketoprofen, ibuprofen	(Agunbiade *et al*. 2015)
			antibiotics	Ampicillin, ciprofloxacin, nalidixic acid, bezafibrate, Fluoroquinolones	(Agunbiade *et al*. 2015)
			Human indicators	Caffeine,	(Agunbiade *et al*. 2014)
	West			No data	
Wastewater	North	0.01-127700	Antiretroviral	12-hydroxy, Nevirapine, 8,14 dihydroxy, Efavirenz, Lamivudine, Emtricitabine, Famciclovir (Famvir)	(Osunmakinde *et al.* 2013): Schoeman *et al.* 2017)
				Lamivudine, Nevirapine, Efavirenz, Ritonavir,Ribavirin	(Osunmakinde *et al.* 2013): Schoeman *et al.* 2017)
			Hormones	7 β-estradiol, 17α ethinylestradiol, 17α-ethinylestradiol, 18 b-estradiol,	(Kanama *et al*. 2018)
			Poly aromatic hydrocarbons	Acenaphthene, Acenaphthylene, Amphetamine, Anthracene, Fluoranthene, Naphthalene, Phenanthrene, Fluorene	(Edokpayi *et al*. 2016)
				Benzo[a]pyrene, Benzo[b]fluoranthene,	(Edokpayi *et al*. 2016)
			UV filters	Benzophenone-3, Benzophenone-4,	(Archer *et al.* 2017)
			Plasticizer	Bisphenol-A	(Archer *et al.* 2017)
			Lipid regulators	Bezafibrate, Atorvostatin	(Archer *et al.* 2017)

Parabens	Methylparaben, Propylparaben Pyrene	(Archer *et al.* 2017)
Steroids	Estriol, Estrone	(Archer *et al.* 2017)
Anti-depressants	Valsartan, Venlafaxine, Desvenlafaxine	(Archer *et al.* 2017)
Diabetes	Gliclazide, Metformin	(Archer *et al.* 2017)
Anti-inflammatory drugs	Ibuprofen, Ketoprofen, Diclofenac, Naproxen	(Archer *et al.* 2017)
personal care products	Triclocarban, Triclosan	(Archer *et al.* 2017)
Analgaesics	Codeine, Tramadol	(Archer *et al.* 2017)
Beta-blockers	Atenolol	(Archer *et al.* 2017)
antibiotic	chloramphenicol, Ciprofloxacin, Clarithromycin, tetracycline, Acetaminophen norfloxacin, Ofloxacin, Sulfamethoxazole, Sulfasalazine, Azithromycin, Trimethoprim,	(Archer *et al.* 2017)
Human indicators	Caffeine, Dextromethorphan	(Archer *et al.* 2017)
illicit drug compounds	Mephedrone,methamphetamine,cocaine,	(Archer *et al.* 2017)
Anti-epileptic	Carbamazepin,	(Archer *et al.* 2017)
Human indicators	Cotinine, Nicotine	(Archer *et al.* 2017)
Alkylphenol ethoxylates	Polybrominated biphenyls-(17), Polybrominated biphenyls-(28), Polybrominated biphenyls-(47)	(Archer *et al.* 2017)
Anti-depressants	Fluoxetine	(Archer *et al.* 2017)

		Antihistamine	Fexofenadine	(Archer *et al.* 2017)
		Drug precusor	Ephrin type-A receptor precursor	(Archer *et al.* 2017)
South	2.59-6596000	antibiotic	acetaminophen	(Archer *et al.* 2017) (Archer *et al.* 2017)
		phenolic compounds & phthalates	2,4,6-trichlorophenol,2,4-dimethylphenol,4-chloro-3-methylphenol,2-chlorophenol, diethyl phthalates, phenol	(Olujimi *et al.* 2012)
		Antiretroviral	Lamivudine	(Mosekiemang *et al.* 2019)
		congeners of PBDE	brominated diphenyl ether (153), Polybrominated biphenyls, brominated diphenyl ether (100), brominated diphenyl ether (154), brominated diphenyl ether (183), brominated diphenyl ether (209), brominated diphenyl ether (28), brominated diphenyl ether (47), brominated diphenyl ether (99), Bisphenol A, DBP, decabrominated diphenyl ether	(Daso *et.al.* 2013: Daso *et.al.* 2012)
		nutrient sources	Ortho phosphate	(Adeleye 2016)

		perfluorinated compounds	Perfluoroheptanoic Acid, Perfluorooctane Acid, Perfluorononanoic Acid, Perfluorodecanoic Acid	(Adeleye 2016)
			Perfluoroundecanoic Acid, Perfluorooctane Sulfonate,	(Adeleye 2016)
		Plasticizer	Bisphenol A	(Adeleye 2016)
East	2-2300000	Steroid hormones	Oestradiol (E2), Oestrone (E1), Ethynyl-oestradiol (EE3), Testosterone,	(Manickum and John, 2014)
		antibiotic	ciprofloxacin, Clarithromycin, Acetaminophen, Nalidixic acid, Erythromycin, Ampicillin, Tylosin, Tetracycline,Sulfamethoxazole	(Madikizela *et al.* 2014)
		Anti-psychotic	Clozapine	(Matongo *et al.* 2015)
		Pharamaceutical	Chloramphenicol	(Agunbiade and moodley, 2014)
		Lipid regulators	bezafibrate	(Agunbiade *et al.* 2015)
		analgesic	Acetylsalicyclic acid, Salicyclic acid	(Gumbi *et al.* 2019)
		Anit-inflammatory drug	Ibuprofen, Ketoprofen, Diclofenac, Naproxen, Aspirin	(Gumbi *et al.* 2019)
		Human indicators	Caffeine	(Agunbiade and moodley, 2014)

Antiretroviral	Darunavir, Emtricitabine, Atazanavir	(Bischel *et al.* 2015)
human metabolite	N4 Acetyl- sulfamethoxazole	(Bischel *et al.* 2015)
Pharamaceutical	Meclofenamic acid	(Gumbi *et al.* 2019)
Diuretic	Hydrochlorothiazide	(Bischel *et al.* 2015)
Anti-epileptic	Carbamazepine	(Gumbi *et al.* 2019)
Beta-blocker	Atenolol, Atenolol acid	(Bischel *et al.* 2015)
hydroxybiphenyls	Pentachlorobiphenyl -101	(Nomngongo *et al.* 2012)
Parabens	Propylparaben	(Nomngongo *et al.* 2012)
Antibacterial	Trimethoprim,	(Bischel *et al.* 2015)
person care product	Triclosan	(Gumbi *et al.* 2019)

2.2 Occurrence of ECs in the water environment of South Africa

2.2.1 Drinking water

The concentration of ECs in drinking water sources from different zones ranged from 0 – 330 ng/L (East zone), 0.03 – 220 ng/L (North zone) and 0– 10 ng/L (South zone) (Table 2). There are no studies so far reported from the West zone. The compounds reported in the highest concentration from the North zone are Terbuthylazine (220 ng/L), Atrazine (160 ng/L), and Carbamazepine (150 ng/L). All these three compounds were also detected in high concentrations from the East zone, however, with Carbamazepine being the highest (330 ng/L), followed by Atrazine (180 ng/L) and Terbuthylazine (60 ng/L). The maximum reported concentration of Terbuthylazine in South Zone was 10 ng/L. Other major ECs reported from the South zone are Estrone (E1), 17b-Estradiol and Ethynylestradiol (Van Zijl *et al.,* 2017).
Though no data is available from the West zone, due to the dominant presence of Atrazine, Terbuthylazine and Carbamazepine in all the other three zones of the country, it is imperative that these compounds be included in the watch list of ECs in drinking water and surface water in South Africa (SA). Due to the absence of EC data from the West zone, more research efforts should be directed towards monitoring the drinking water source in this zone, making it easy to comprehend the level of EC pollution and planning for its mitigation.

2.2.2 Groundwater

Groundwater sources are inadequately monitored for the occurrence of ECs in South Africa. So far, there is only one study that reported the presence of ECs in groundwater from the North zone (Rimayi *et al.,* 2018). In their study, 11 ECs were detected from groundwater samples collected near the Hartbeespoort Dam in Gauteng province, with the anti-retroviral drug Nevirapine being the most abundant compound, with a concentration of 13 ng/L. South Africa rely on surface water for the majority of its freshwater supply, which probably justifies the abundance of literature on EC monitoring in surface water. Post democratisation in 1994, groundwater has become an essential source of potable water for livelihood to 50% of the population living in villages and small towns (WRC, 2017).

A national-level strategic framework has been established by the department of water and sanitation in the country to explore the full potential of groundwater and initiate its sustainable utilisation within national water resource management (WRC, 2017). A fundamental focus of the groundwater strategy is to provide a proper valuation to this neglected resource and establish its conservation, protection and sustainable use. Furthermore, efforts have also been made to investigate groundwater sources and their delineation in the country to establish a protection roadmap and its sustainable usage (WRC, 2018). These recent efforts towards integrating groundwater as an essential component of water supply in South Africa warrants the need for monitoring EC pollution in groundwater sources in the country.

2.2.3 Surface water

ECs that have been reported from surface water across South Africa are listed in Table 1. Compounds that are detected in high concentrations from the North zone includes herbicides and antiretroviral drugs (ARVs) in the following order: Terbuthylazine (1969 ng/L)>Nevirapine (1480 ng/L) >Atrazine (1237 ng/L)>Zidovudine (973 ng/L) >Stavudine (778 ng/L) (Figure 3) (Rimayi et al., 2018; Wood et al., 2015). The highest concentrations of Terbuthylazine and Atrazine are reported from the catchment of the Hartbeespoort Dam while Nevirapine, Zidovudine and Stavudine are reported in high concentrations from the Roodeplaat Dam. The concentration of compounds detected from the East zone are in the following order: Aspirin (44243 ng/L)> Fluoroquinolones (27100 ng/L) >Atenolol (25900 ng/L)>Nalidixic acid (25234 ng/L) >Ciprofloxacin (20514 ng/L) (Figure 3) (Agunbiade *et al.*, 2014). Most of these compounds are reported from the Msunduzi River in Pietermaritzburg except for Atenolol, which was found high in Umgeni River, Durban. Wood et al. (2015) investigated the level of Caffeine and twelve antiretroviral drugs in Eerste River, Waterkloof Dam, in the South zone and Vaal dam in North zone. Among the different ECs analysed, Caffeine and Zidovudine are the only ECs detected from the Vaal dam with maximum concentration levels of 158 and 52 ng/L, respectively (Figure 4). In Western Cape, i.e., south zone, few rivers (Diep River, Salt River and Eerste River) have been monitored for the presence of Perfluorooctanoate (PFOA) and Perfluorooctane sulfonate (PFOS). The maximum concentration reported was 314 ng/L and 182 ng/L (Diep River), 390ng/L and 47 ng/L (Salt River) and 146 ng/L and 23 ng/L (Eerste River), respectively (Mudumbi, 2012; Mudumbi et al., 2014).

A common source of Caffeine in surface water bodies is the effluent from WWTPs, which may be the reason for its high presence in surface water (Buerge *et al.*, 2003). The ARV drugs, Zidovudine and Nevirapine are the highest detected compounds from the North zone (Figure 3). In addition, Zidovudine and Nevirapine are not effectively removed in wastewater treatment plants (WWTPs) (Prasse *et al*., 2010), which may be another reason for the increased concentration of these compounds in surface water. Both these compounds are used in South Africa in combination therapies such as Highly Active Antiretroviral Therapy (HAART). Sources of ECs in surface water can be speculated by correlating consumption patterns of the ECs and their occurrence in the surface water. Caffeine is used as an anthropogenic pollution marker due to its wide consumption among humans and its positive correlation with other ECs may indicate the sources and consumption patterns of ECs in the target population (Buerge et al., 2003; Wood *et al.*, 2017). However, Wood *et al*. (2015) did not find a correlation between the concentrations of 12 ARVs and caffeine in the North, East and South zones surface water samples. This indicates that the consumption of ARVs might not be uniform in all regions of South Africa, or different compounds are removed differently in WWTPs, or the limitations of using caffeine as a biomarker for monitoring EC pollution.

The limitations of using caffeine as an anthropogenic biomarker is related to its non-stability in water systems, different partitioning to solid matrix and release of caffeine from different sources to the environment. For example, caffeine sources in the surface water can be runoff from coffee grounds, leachate from garbage disposals and dumping of caffeinated drinks into drainage systems (Senta *et al.*, 2015). Senta *et al.* (2015) have reported good agreement of caffeine metabolites 1-methylxanthine and 7-methylxanthine (Paraxanthine) with population size estimations in Italy. However, more information about different sources of these biomarkers in the sewage and their elimination in the WWTPs is necessary to derive conclusions from their correlations with other ECs. Therefore, these findings should be considered while speculating about the sources of ECs in surface waters of South Africa. There is no data available in the literature regarding the presence of ECs in rivers from the West zone. However, in Vaal River (principal tributary in the (Orange River basin), the presence of ARVs and pharmaceuticals have been reported from the upstream in North West province (North zone), and downstream in Western Cape (South zone) (Chokwe *et al*., 2015; Wood *et al.*, 2015). Nevertheless, it is important to note that there are several tributaries (the Harts River, the Riet River, the Modder River, and the Seekoei River) to the Vaal River that flows within the West zone, which has not been investigated for ECs.

This indicates a reasonable knowledge gap concerning EC pollution in surface water sources of the West zone and the contribution of various tributaries to the EC pollution in the Vaal River.

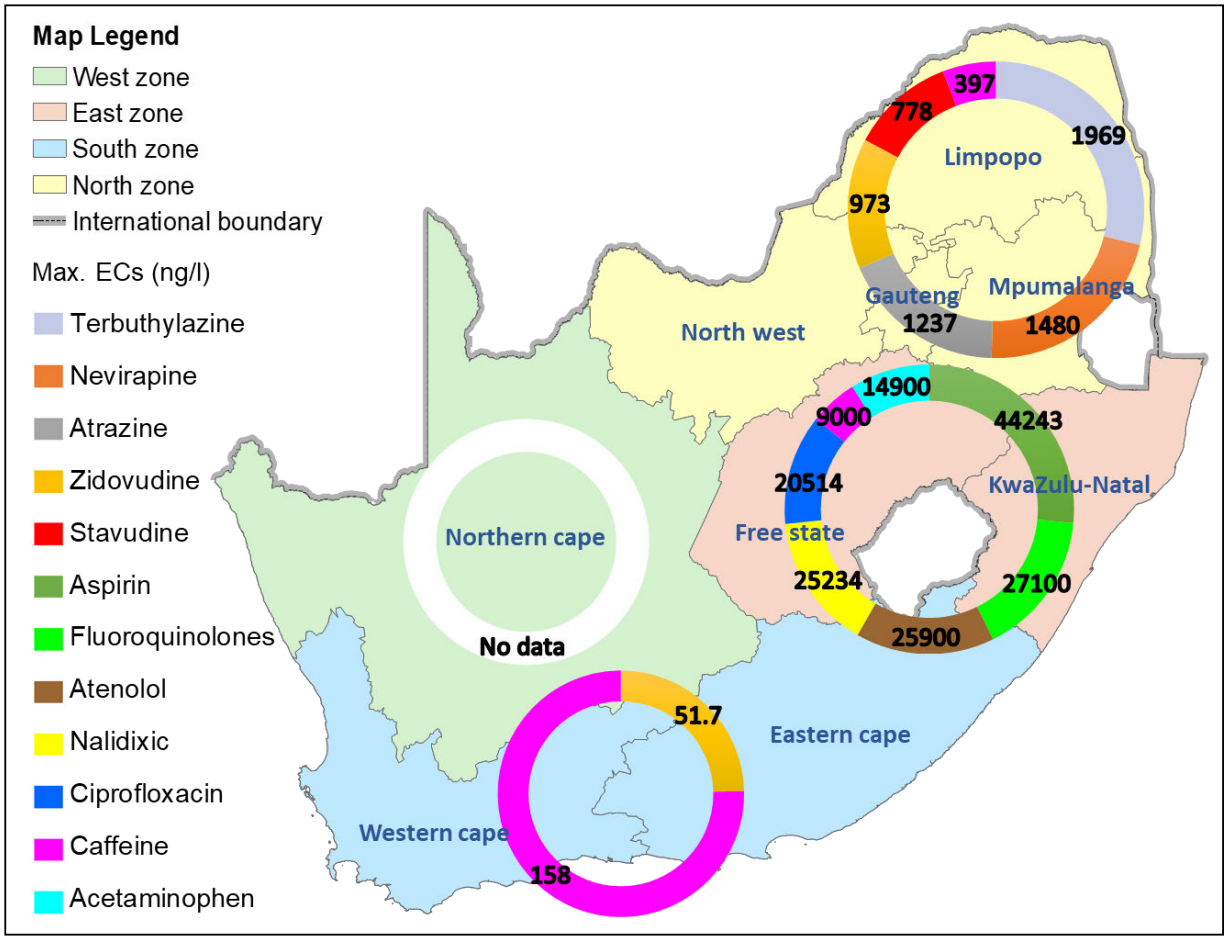


Figure 4: Contamination map of various ECs in the freshwater of South Africa. Twelve compounds having the highest concentration from all selected zones are plotted in respective geographical zones.

Table 2: Overview of EC contamination in drinking water sources of South Africa.

North zone		**Reference**
Types of chemicals present	Pharmaceutical, Antivirals, Steroid hormones	(Patterton, 2013), (Odendaal *et al.* 2015)
Range of ECs (ng/L)	0.02 -220	
Average max. concentration (ng/L)	97	
Compound in maximum concentration (ng/L)	Atrazine, Terbuthylazine, Carbamazepine, 160, 220, 150, respectively.	
South zone		
Types of chemicals present	Pharmaceutical, Steroid hormones	(Patterton, 2013)
Range of ECs (ng/L)	0 - 10	
Average max. concentration (ng/L)	1.5	
Compound in maximum concentration	Terbuthylazine (10 ng/L)	
East zone		
Types of chemicals present	Pharmaceutical, Steroid hormones	(Patterton, 2013), (Odendaal *et al.* 2015)
Range of ECs (ng/L)	0 -330	
Average max. concentration (ng/L)	82.16	
Compound in maximum concentration	Atrazine (180 ng/L), Terbuthylazine (60 ng/L), Carbamazepine (330 ng/L)	

2.2.4. Wastewater

The ECs present at high concentrations in untreated wastewater in South Africa included a wide range of compound categories such as antipyretics, pharmaceuticals, personal care products (analgesics/anti-inflammatory drugs, antibiotics) and phthalates (Figure 5). In the North zone, Triclosan (128 µg/L), Ibuprofen (112 µg/L), Naproxen (55 µg/L), (Amdany *et al*., 2014), Acetaminophen (50 µg/L) (Kanama *et al.,* 2018) and Efavirenz (13 µg/L) (Schoeman *et a*l., 2017) are reported in high concentrations. In the South zone, Diethyl phthalates (DEP) (6596 µg/L), Dibutyl phthalate (DBP) (5267 µg/L), Benzylbutyl phthalate (BBP) (846 µg/L), Diethylhexyl phthalate (DEHP) (3917 µg/L), and Pentachlorophenol (PCP) (843 µg/L) are reported in high concentrations in untreated wastewater (Olujimi *et al.*, 2012). From the East zone, compounds such as Aspirin (118 µg/L), Ibuprofen (69 µg/L), Salicyclic acid (66 µg/L), Sulfamethoxazole (SMX) (34.5 µg/L) and Triclosan (30 µg/L) are reported in high concentrations (Agunbiade *et al.*, 2015; Gumbi *et al.*, 2019; Madikizela, and Chimuka, 2017). However, no published data is available from the West zone.

Based on the presence and concentration levels, compounds shown in Figure 4 can be suggested as a priority list for the regulatory framework for future WWTP monitoring programme in South Africa. Phthalates, DEP, DBP, BBP and DEHP are found at high concentrations in all four zones. It was also noticed that the reported Phthalate concentration in the untreated wastewater in South Africa is higher than the concentration reported from other countries, especially in domestic wastewater. Phthalates for their low melting point (below -25^{o}C) are used as plasticisers in plastics (Staples *et al.,* 1997). The concentration of DBP in untreated wastewater has been reported as 20.84 µg/L and 1.10 - 4.99 µg/L in Denmark and Paris respectively (Berge *et al.,* 2014; Roslev *et al.,* 2007). Gani *et al.* (2016a) reported the concentration of DEP and DBP in fifteen WWTPs of India within the range of 2.184- 83.470 µg/L and 0.928-19.721 µg/L respectively, which was equivalent to their occurrence level reported from China (Gao *et al*. (2014) and France (Clara *et al.,* 2010). DEP is a common ingredient in personal care products such as long fragrance agent in scents and perfumes. It is also reported to be used in 67 cosmetic preparations including bath preparations, toilet waters, hair sprays and skincare products (Kamrin & Mayor, 1991). Similarly, DBP is used in cosmetic products such as nail polish to remove its chipping feature (IARC 2000). It is also widely used in the preparation of specific adhesives and cellulosic coatings.

In different countries, the maximum DEHP concentration has been reported as, 467 µg/L (France), 43.9 µg/L (Denmark), 34 µg/L (Austria), 30.99 µg/L (China) and 23.6 µg/L (UK) (Gani et al., 2016b). BBP and DEHP are important components for plasticity during the manufacture of polyvinylchloride products (Lassen et al., 2009). DEHP being a cheaper and effective plasticiser are often used in toys and may pose an early exposure of children to this toxic compound (USEPA, 2007). The above wide applications of these compounds in the manufacturing industries may have contributed to their highest occurrence level in WWTPs as the effluent from these industries is generally discharged to the urban WWTPs. Therefore, an initiative to control at the source and removal in WWTPs should be emphasised to protect our limited surface water resources from these harmful chemicals. However, WWTPs in South Africa have not been investigated for phthalate removal, which highlights the need for its inclusion in future research programmes. In addition, the United States Environmental Protection Agency (USEPA) and the European Union have listed phthalates as a priority list of hazardous substances and banned their usage in toys and baby products (USEPA, 2007).

The majority of the ECs in the environment is from anthropogenic sources, whereas hormones such as estrogens in the water environment originate from both natural and man-made sources (Servos et al., 2005). The common natural estrogens present in wastewater such as estrone (E1), 17β-estradiol (E2) and estriol (E3) are released from the human body, whereas synthetic estrogen, 17α-ethynilestradiol is predominantly used as a synthetic compound in birth control drugs (Zheng et al., 2008). Both natural and synthetic steroids have high potency on endocrine system disruption. The data indicate that both the natural and synthetic estrogens are present in lower concentrations compared to pharmaceuticals in wastewater across South Africa. A study conducted in the Northwest province has shown that among the different estrogens, 17α-ethinylestradiol is found in high concentrations (5.6 µg/L) in the influent of WWTP receiving wastewater from the nearby hospitals (Kanama et al., 2018). They further noted that even the concentration of 17α-ethinylestradiol (EE2) in the treated effluents is more than the concentration of other estrogens in untreated influents. They reported an average EE2 concentration of up to 1.34 µg/L in the effluent, while the concentration of Estrone (E1), 17 β-estradiol (E2) and Estriol (E3) in the untreated influent were 0.031 µg/L, 0.023 µg/L, and 0.463 µg/L respectively. To assess the quality of water bodies by monitoring estrogenic activity, gene-based assays are proven very useful. The estrogenic activity is represented as effect-based trigger (EBT) values in terms of 17β-estradiol equivalents (EEQs) (Snyder et al., 2001).

The EBT values for *in vitro* estrogenic activity in water samples has been reported in the range of from 0.1 to 1.01 ng EEQ/L (Brion et al., 2019) indicating the possibility of estrogenic activity in the samples reported by Kanama *et al.* (2018). A higher concentration of EE2 in the final effluent suggests its persistence during the different stages of the treatment process and could be used as an indicator compound for monitoring estrogens in the South African wastewater. EE2 is an established anthropogenic pollutant that has a high potency on endocrine systems at lower concentrations than other steroids and/or ECs. However, there may be much more variation in the usage pattern of EE2 between urban, peri-urban and rural locations which need to be considered in monitoring plans.

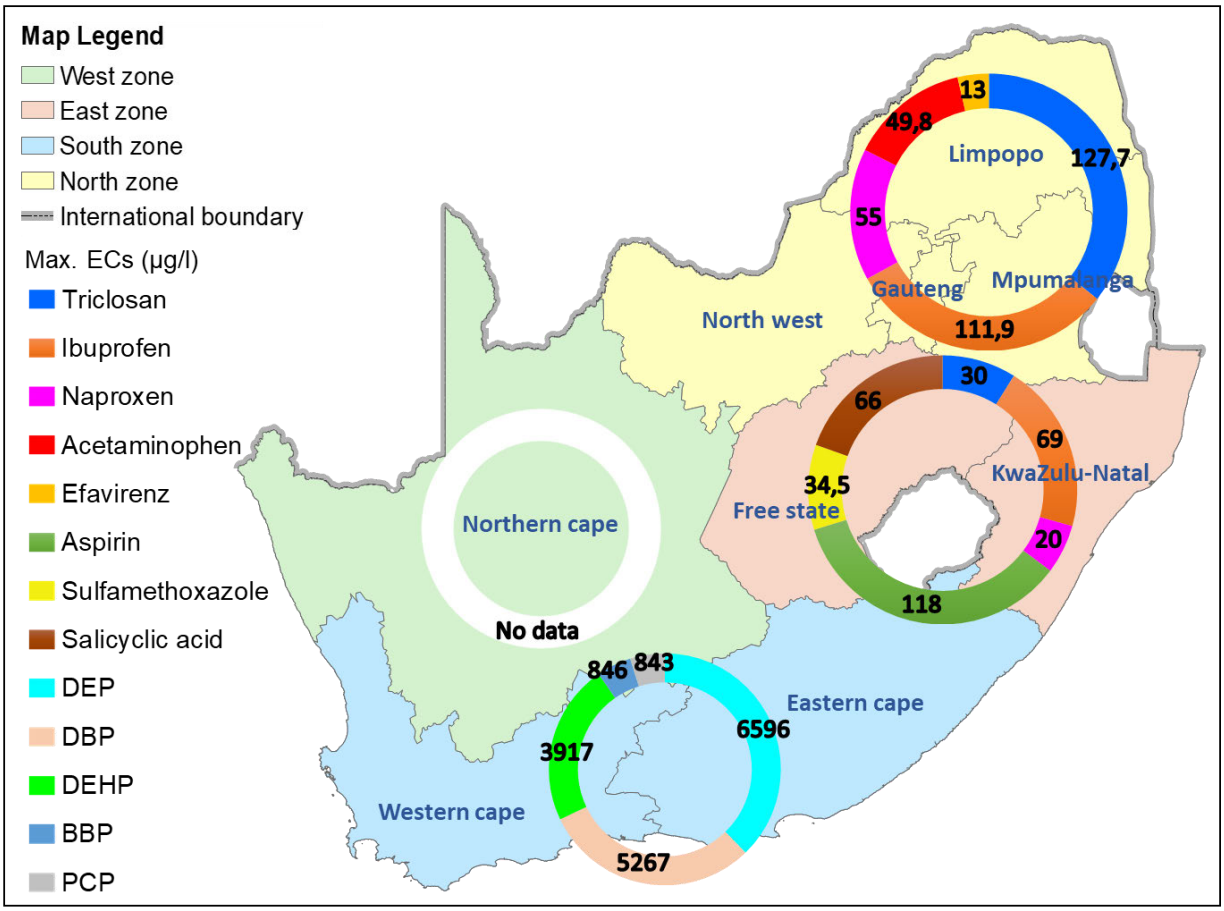


Figure 5: Contamination map of various ECs in untreated wastewater of South Africa. The map shows compounds from each zone having the highest concentration.

2.3 Comparative assessment of ARVs in South African water environment with global data

Antiretroviral drugs are used to treat HIV through highly active antiretroviral therapy (HAART). There are more than 35 ARVs that are being used for HIV treatment, which includes drugs such as Abacavir, Efavirenz, Emtricitabine, Lamivudine and Zidovudine (International Pharmaceutical Manufacturers and Associations, 2017). The combination therapies of these drugs are reportedly more suitable for fragile patients, adolescents, and pregnant women. Due to the world's largest ART programme, the consumption of ARVs per capita is highest in South Africa than any other country (WHO, 2013). Therefore, in this review, a comparative assessment of ARV data obtained from the South African aquatic environment and global studies were performed. The available literature from South Africa and other countries are compiled and listed in Tables 25 Appendix 2 and are discussed in the following subsection:

2.3.1 Surface water

In literature, very few studies have focused on the occurrence of ARVs in South African freshwater systems (Table 25 Appendix 2) According to Wood *et al*. (2015), among the different ARVs, Abacavir was not detected from freshwater systems in South Africa. However, it was reported from Germany and France at a concentration of 1.4 and 2.6ng/L, respectively (Prasse *et al.,* 2010; Dévier *et al*., 2013). According to Rimayi *et al.* (2018), Efavirenz and Emtricitabine concentrations in South African rivers were 354 and 13 ng/L, respectively. Lamivudine and tenofovir are the most used ARVs in South Africa (González, 2019). Wood et al. (2015) reported a much higher concentration of Lamivudine (242 ng/L) in the surface water of South Africa, in comparison to some European and Asian countries. For example, 4-9 ng/L in Japan (Azuma et al., 2015); 20 ng/L in Germany (Boulard et al., 2018); 12 ng/L in Finland (Ngumba *et al*., 2016b) and 4.1ng/L in France (Aminot *et al*., 2015) have been reported. In contrast to the above studies, in Kenya, a much higher concentration (167,100 ng/L) of Lamivudine in surface (river) water was reported (K'oreje *et al*., 2016). The highest Nevirapine levels reported in South African surface water is 1,480 ng/L (Wood et al., 2015). However, higher levels (5,620 ng/L) of Nevirapine in Kisumu, Kenya was reported by K'oreje et al. (2016).

With 5 per cent of the population living with HIV infection, Kenya too has an ART program which was started in 2015, and more than 1 million people have accessed the treatment (UNAIDS, 2017). Lamivudine and Nevirapine being the first-line regimen drugs in Kenya may justify their higher levels in surface waters (UNAIDS, 2017). In contrast, from European countries, France for example, very low levels (1.3±0.6 ng/L) of Nevirapine was reported (Aminot et al., 2015), while it was not detected in Finland (Ngumba et al., 2016). Zidovudine concentration in South African surface water was around 973 ng/L (Wood et al., 2015), however in Kisumu, Kenya it was detected in much higher concentration (17,410 ng/L) (K'oreje *et al*., 2012). Nevertheless, the maximum levels of Zidovudine in European surface water were reported from Germany with 170 ng/L (Prasse et al., 2010) which was followed by France (33 ng/L) (Aminot et al., 2015). In developing countries, due to the lower levels of sanitation, contamination of the surface water bodies is common. More than 90% of sewage produced in developing countries is discharged untreated into the rivers, polluting the vital resource (Langergraber and Muellegger, 2005). Together with large ARV programs in South Africa, the huge difference in the sanitation facilities between developing and developed countries may pronounce the differences in the ARV contamination in their surface water sources.

2.3.2 Drinking water and groundwater

Regarding the presence of ARVs in drinking and groundwater, there are only a few studies conducted in South Africa so far. Swanepoel et al. (2015) reported Abacavir and Lamivudine at a concentration of < Limit of Quantitation (LOQ) (0.02 ng/L) and <LOQ (1 ng/L) respectively, in groundwater in the North West and Gauteng Provinces of South Africa, which are lower than reports from other countries. For example, Boulard et al. (2018) reported a high concentration of Abacavir (up to 11 ng/L) in Koblenz groundwater, Germany. Similarly, higher values of Lamivudine in Groundwater were reported from USA (25,2 ng/L) by Fisher et al. (2016) and Germany (1,8 ng/L) by Boulard et al. (2018). In addition, Furlong et al. (2017) reported Lamivudine level of 4 ng/L from a drinking water treatment plant in the USA, and Boulard et al. (2018) reported a Lamivudine concentration of <1 ng/L in treated drinking water in Germany. A high concentration of Nevirapine (13 ng/L) in South African Groundwater near Hartbeespoort Dam catchment (Gauteng province) was reported by Rimayi et al. (2018).

However, much higher values of Nevirapine was reported from groundwater in the USA (27.73 ng/L by Fisher et al., 2016) and Kenya (1600 ng/L by K'oreje et al., 2016). The Nevirapine level reported from drinking water in South Africa was <LOQ (92.7) ng/L (Wood *et al.*, 2015). A concentration of Zidovudine up to <LOQ (0.3) ng/L) was reported in the Groundwater of Northwest and Gauteng Provinces, South Africa (Swanepoel *et al.*, 2015). However, higher values of Zidovudine (30 ng/L) were detected in the Groundwater in Kisumu, Kenya (K'oreje et al., 2016). Comparatively higher Zidovudine levels (72.7 ng/L) were reported from Tap water at Hartbeespoort Dam in South Africa (Wood et al., 2015). From these studies, it can be deduced that the concentration of ARVs in drinking water and Groundwater of South Africa are lower than that of global averages. Considering the highest ARV consumption in South Africa than other countries and its concentration in WWTPs and surface water, the above studies are insufficient to draw a conclusion regarding their comparative presence in drinking water and groundwater. Therefore, more studies need to be directed towards EC monitoring in general and ARVs in particular, in groundwater and drinking water sources in different geographical zones of South Africa.

2.3.3 Wastewater

The maximum concentrations of ARVs in sewage influent and effluent from various regions in South Africa and abroad are included in Table 26 Appendix 2. According to Abafe *et al*. (2018), the Abacavir concentration in the influent of the selected South African WWTPs (East zone) ranged from 3,500±210 to 14,000±2300 (ng/L). However, the reported Abacavir levels in the influent of WWTPs in countries like Germany were far lower than that of South Africa, with a maximum average concentration of about 255±40 ng/L (Prasse *et al.*, 2010). Regarding the occurrence of Efavirenz drug, Abafe *et al.* (2018) reported the highest average concentrations for both influent and effluent of a selected WWTP in KwaZulu Natal province (East zone) was around 34,000±1900 and 20,000±2000 (ng/L) respectively. In Kisumu (Kenya), K'oreje *et al*. (2016), indicated the presence of Efavirenz to a maximum average concentration of up to 1,020 ng/L in the influent and 110 ng/L in the effluent of a WWTP. Similarly, Funke *et al*. (2016), reported a high concentration of Emtricitabine in the sewage influent in Germany, with a maximum average concentration of 980±50 ng/L. These levels were far higher than those reported in the sewage influent (172 ng/L) of Western Cape (South zone), South Africa (Mosekiemang *et al*., 2019).

Similarly, Mosekiemang *et al.*, (2019), reported a Lamivudine average of about 20.9 ng/L in Western Cape (South zone) sewage influent, while Abafe *et al*. (2018) reported a much higher level (2,200 ± 190 ng/L) from the sewage influent in KwaZulu-Natal (East zone). In Germany, Prasse *et al.* (2010) reported 720±130 ng/L Lamivudine from sewage influent, while K'oreje et al. (2016) narrated far higher Lamivudine levels from both influent (60,680 ng/L) and effluent (31,070 ng/L) samples in Kisumu, Kenya. Additionally, Aminot et al. (2015) and Vergeynst et al. (2015) reported Lamivudine concentrations of 55 and 507±80 ng/L in France and Belgium, respectively. The maximum average concentrations of Nevirapine were reported from the Phoenix WWTP in KwaZulu-Natal (East zone) South Africa, with 2,800±190 and 1,400±63 ng/L for influent and effluent respectively (Abafe *et al*., 2018). In contrast, much lower levels (53 and 92 ng/L for influent and effluent respectively) were observed in Kitate, Gauteng (Schoeman et al., 2017). In Kisumu, Kenya, K'oreje et al. (2016) reported Nevirapine concentrations of 3,300 and 2,110 ng/L for influent and effluent, respectively. However, very low values were detected in Germany (21.8±2.3 ng/L) and Finland (19 ng/L) in sewage influent (Prasse et al., 2010; Ngumba et al., 2016), respectively.

In the study by Mosekiemang *et al.* (2019), the drug Zidovudine was not detected in the sewage samples from Western Cape, South Africa. In contrast, in KwaZulu-Natal, South Africa, Abafe et al. (2018) reported high levels of Zidovudine in sewage influent and effluent with the maximum average of 53,000±3,600 and 500±86 ng/L, respectively. Given the ART program is common across South Africa, the geographical differences in the concentration of Zidovudine may be due to the grab sampling approach adopted in the two studies. However, the reported Zidovudine levels in the WWTP influent of other countries were 62 ng/L in Finland (Ngumba et al., 2016); <LOQ in China (Peng et al., 2014); 390 ng/L in Germany (Funke et al., 2016) and 20,130 ng/L in Kenya (K'oreje et al., 2016). These results indicate wide differences in the occurrence of different ARV drugs in WWTPs within the different geographical zones of South Africa as well as in other countries. This variation could have originated due to the differences in the prevalence and usage of these drugs within the linked communities as well as the detection methods employed. Further, the different wastewater treatment processes and the operational parameters could impact the removal of ECs from wastewater. Therefore, future research should focus more on understanding the impact of various operational parameters on the fate and removal mechanisms of ECs from wastewater.

2.3.4 Research gaps and possible research questions in comparative assessment of ARVs in South African water environment with global data

The comparative assessment of ARVs in the South African water environment in comparison to global data has revealed several research gaps and raised important research questions:

- Regional disparities in ARV Concentrations: One of the significant research gaps identified is the regional disparities in ARV concentrations in South African water systems compared to other countries. To understand the factors contributing to these differences and the potential risks associated with these variations, further investigation is necessary.
- Factors influencing concentration differences: Research should delve into the factors that contribute to varying concentrations of ARVs in South African water sources. This includes understanding the role of sanitation facilities and practices, especially in developing countries, and their impact on ARV contamination in surface water.
- Sanitation infrastructure improvement: Inadequate sanitation infrastructure in developing countries has been identified as a critical factor leading to higher ARV contamination levels in surface water. This underscores the need for research focusing on improving sanitation facilities in these regions to mitigate the environmental and human health implications of ARV contamination in water bodies.
- Presence of ARVs in drinking water and groundwater: The absence of comprehensive data on the presence of ARVs in South African drinking water and groundwater sources is concerning. Research is needed to assess the potential exposure to these drugs through drinking water and the health implications for individuals consuming water from these systems.
- Wastewater treatment optimization: The effectiveness of wastewater treatment processes and operational parameters significantly influences the release of ARVs into the environment. To safeguard human health and ecosystems, research should aim to optimize wastewater treatment to reduce ARV contamination and mitigate its consequences for the environment.

These research gaps and questions highlight the importance of further investigations into the presence and impact of ARVs in South African water systems and underscore the need for research to address regional disparities, improve sanitation infrastructure, and optimize wastewater treatment processes for the benefit of human and environmental health.

2.4 Risk assessment of ECs

Most of the reported EC related studies in South Africa have focused on their occurrence and removal aspects, with little or no risk assessment studies conducted so far. Consequently, in this review, an attempt was made to perform an environmental risk assessment of ECs present in surface waters of South Africa based on available data. The environmental risk of ECs was assessed by calculating a risk quotient (RQ) from the reported maximum concentration of a compound against a predicted no-effect concentration of the most sensitive test organism/s, sometimes at varying trophic levels (Figure 6). RQ is the ratio of the measured environmental concentration (MEC) of an EC in surface water and predicted no-effect concentration (PNEC). High, medium and low risk for a test organism are indicated by an RQ value equal to ≥ 1, 0.1 to 1, and <0.1 respectively. RQ is based on the assumption that the detected environmental concentrations and acute toxicity of ECs to non-target organisms are crucial to identify their level of risk. Accordingly, three organisms Algae (phototrophic level), Crustaceans (invertebrates) and Fish (vertebrates) of different trophic levels in aquatic ecosystems were selected to evaluate the possible eco-toxicological impact of detected ECs in surface water (European Commission, 2003). PNEC values of ECs for the above three organisms were calculated from the reported acute toxicity data (LC50 and EC50 divided by an assessment factor) Table 27 Appendix 2 (Zhoua *et al.*, 2019). For those compounds where there was no toxicity data reported, direct PNEC values were obtained from the literature. Lowest PNEC values among the three organisms were selected to calculate RQ to assess the worst-case scenario of the risk.

A mixed response was obtained after the calculation of RQ for the reported maximum concentration of ECs. RQ of ECs such as Aspirin, Acetaminophen, Carbamazepine, Clarithromycin, Atrazine, Streptomycin, Fluoxetine, Erythromycin, Ibuprofen, Ciprofloxacin, Ampicillin, Stavudine and Diclofenac was greater than 1 (Figure 6). The RQ values ranged from 2 to a several-fold increase up to 12366. Of the 32 compounds evaluated, only twelve compounds showed RQ value lower than 1 (Figure 6) which could be of great concern due to the potential risks involved. Moderate risk (0.1>RQ>1.0) was also observed for eight compounds which could also highlight long-term toxicological risks, granted that the EC has a high bioaccumulation potential. RQ of Diclofenac was the highest and was in the range of 100 -12366, for all the datasets reported.

It is important to note that the concentration of Diclofenac in the surface water was listed in the 10th position with respect to their concentration to other ECs present in surface waters of the North and Eastern zone. However, its RQ was greater than the RQ of Aspirin (2.3), the compound that had the highest concentration (44243 ng/L) in surface water (Wood *et al.*, 2015). Similarly, the RQ of caffeine was greater than 1 at two sampling locations, out of a total of nine locations detected. These results highlight the importance of incorporating toxicity assessment in deciding the priority compounds for monitoring and regulations in surface water.

Diclofenac is the most ubiquitous anti-inflammatory drug detected in surface waters of Europe with a mean concentration of 514 ng/L and 1022 ng/L in Spain and Germany respectively (Zhou *et al.*, 2019). Diclofenac and Caffeine are non-steroidal anti-inflammatory drugs (NSAIDs) that are used for the treatment of common symptoms such as inflammation, pain-relieving and fever in human beings (Madikizela and Chimuka, 2016). Approximately 10 per cent of their consumption is excreted by human beings in an un-metabolised form (Kermia *et al.*, 2016), which may be their possible pathway to domestic WWTPs and then into surface waters.

NSAIDs are easily available over the counter in South Africa (SA news, 2018) that increases their chances of wide consumption among the communities. Furthermore, disposal of expired or unused drugs in flushed toilets, a common practice in South Africa, also contributes to their occurrence in surface water. The acceptable concentration of Diclofenac in surface water has been proposed as 100 ng/L by the EU watch list, however, a far higher concentration has been reported from the North zone (300 – 2200 ng/L) and the East zone (600-15600 ng/L) of South Africa. As groundwater is recharged from surface water, the risk associated with ECs in surface water could be a concern, as the groundwater is recharged from surface water and used for direct drinking purpose. The knowledge about the occurrence level and sources of these high-risk compounds should be emphasised so that appropriate environmental policies could be developed for the regulation of these emerging contaminants in surface water.

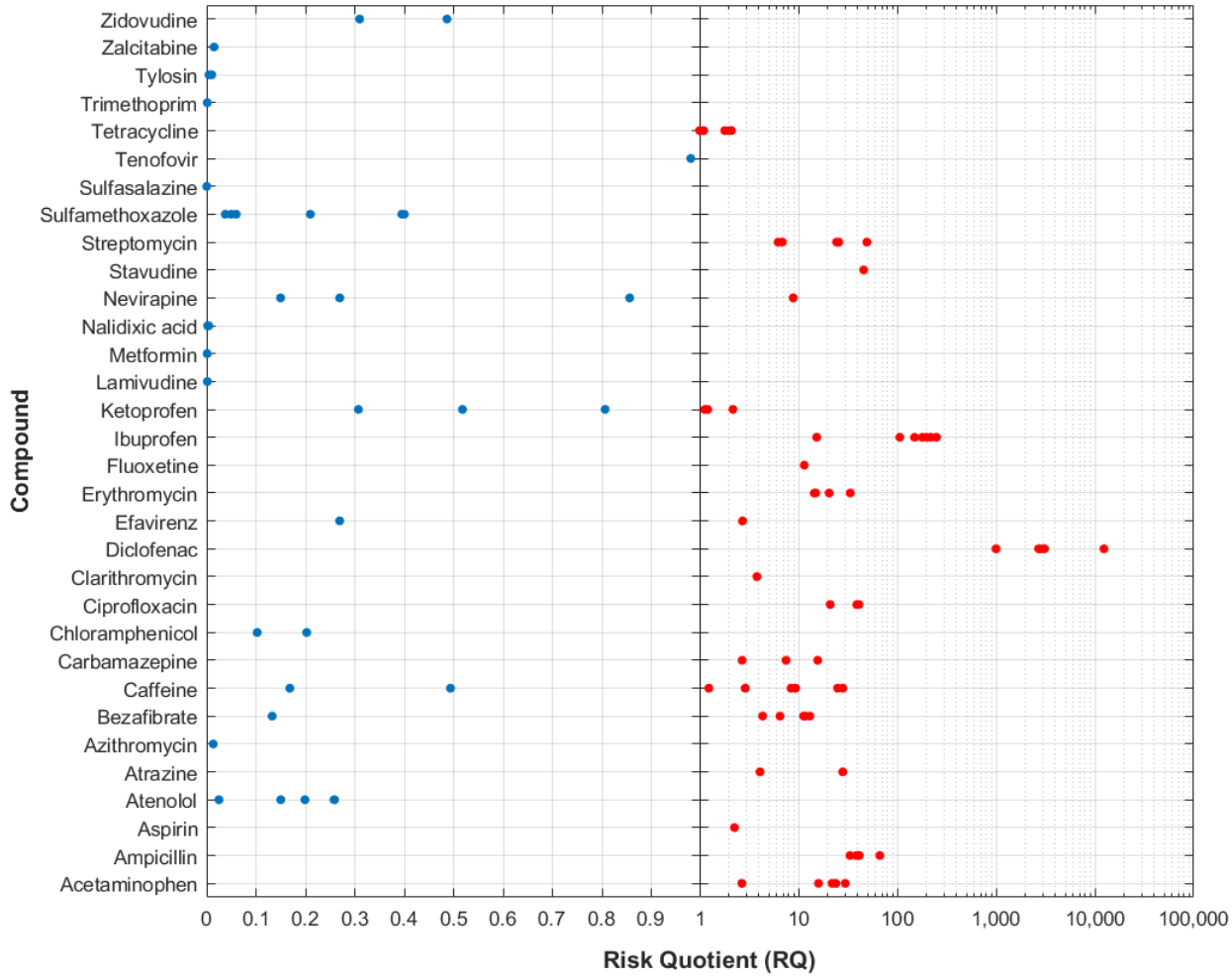


Figure 6: Risk quotient (RQ) of ECs present in surface water of South Africa. RQ is calculated for the reported maximum concentration of each compound.

2.5 Removal of ECs in South African WWTPs

In South Africa, the demand for water in municipal sector applications is 26% of the national available water, and it is annually growing at 1% (WWF, 2017). The sewage generated from this much of municipal sector applications is discharged into nearby water bodies after treatment in a WWTP. However, many WWTPs in South Africa are poorly managed and does not comply with national discharge standards (Herbig and Meissner, 2019). De Klerk, (2019) after a survey, reported that 51 out of 108 WWTPs do not treat wastewater satisfactorily in South Africa. This latest survey also showed that 55% of the WWTPs that discharge along the Vaal River are not in compliance with the national discharge regulations.

The Green drop initiative commissioned in 2008 in South Africa promote excellence in wastewater treatment operation and management by incentive-based regulations and benchmarking. According to national green drop reports, there is a further decline of 5% (52% to 47%) in 2019, which indicated the continuous deterioration of the wastewater management in South Africa (de Klerk, 2019).

The removal performance of ECs in South African WWTPs was reviewed based on the available reports mentioned in Table 28 Appendix 2. An inference from figure 5 is that the highest percentage removal of compounds was observed in studies with only one dataset. For example, out of 35 compounds, 22 compounds showed more than 70% removal efficiency in samples with only one reported dataset. As the number of datasets increased to seven, the average removal efficiency has decreased below 40% (Figure 7). This indicates that the removal efficiencies reported by short term sampling can be misleading. A large number of the dataset is therefore required to conclude the EC removal performance of WWTPs and a variety of other factors such as grab versus composite sampling, different hydraulic retention times of the WWTP, variable mass loadings of ECs need to be considered while reporting EC removal efficiencies of WWTPs (Baalbaki et al., 2017). Zone wise box-plots showed that the median performance removal of ECs ranged from 70 – 85% (Figure 33a Appendix 3), which may indicate satisfactory performance by South African WWTPs in terms of EC removal. However, Polybrominated diphenyl ethers (PBDE) congeners (PBDE17, 28, 47) and antiretrovirals removal percentage varied from 0-100% in South African WWTPs (Figure 33b Appendix 3), making it difficult to conclude the removal efficiency for different ECs. Consistent removal of more than 65% is reported for anti-inflammatory drugs such as Acetaminophen, Diclofenac, Ibuprofen, Ketoprofen and Naproxen (Amdany et al., 2014; Kanama et al., 2018; Madikizela and Chimuka, 2017) while more than 85% removal was reported for some personal care compounds (Triclocarban and Triclosan) (Lehutso et al., 2017). Few WWTPs in Western Cape (South zone) and Gauteng (North zone) have been investigated for the removal of different antiretroviral drugs, namely: 12-hydroxy Nevirapine, Lamivudine, Efavirenz, Emtricitabine, Famciclovir (Famvir), Nevirapine, Ribavirin, and Ritonavir (Mosekiemang *et al.*, 2019; Schoeman *et al.*, 2017). Among these, Schoeman *et al.* (2017) reported a higher removal of Efavirenz (94.5%) and lower removal of Nevirapine (22.5%) in a pre anoxic –oxic treatment configuration based WWTP.

They have also indicated higher Nevirapine concentrations in the post chlorinated effluent (480 ng/L) as compared to the influent (200 ng/L) in few samples, which indicated the role of alternate factors such as de-conjugation of its hydroxylated metabolites in WWTP. Mosekiemang *et al.* (2019) also reported a similar increase in the concentration of Efavirenz and Emtricitabine in the chlorinated effluents of an MBR based WWTP. The authors reported advance tertiary treatment by UV- radiation effective than chlorination, particularly with a concern of the increase in the concentration of compounds after chlorination. The later may be more likely due to non-optimised dosing of the oxidant as the affinity of the chlorine towards the dissolved organic matter is more than residual antiretroviral drug (Acero *et al.*, 2010). The non-optimal operation of the WWTP can also cause the release of the EC incremental mass loadings at post-treatment (Wood *et al*., 2016). The EC removal efficiency of WWTPs, therefore, should be measured in conjunction with metabolites and its transformation product removal. Some metabolites such as hydroxydiclofenac and paraxanthine may prevail in much higher concentrations than their parent compounds, with little knowledge on their potency on non-target organisms. While some metabolites can be more persistent than their parent compounds, for example, biodegradation product of nonylphenol ethoxylates, nonylphenol etc. (Boxall *et al.*, 2004). This characteristic may feature these metabolites as an EC which are not monitored and have unknown toxicological risks. However, there is a lack of information on metabolite formation in the treatment processes and their concentration in the receiving environment. To make a comprehensive evaluation of the contamination scenario, future monitoring studies should focus more on determining parent as well as metabolite formation and removal.

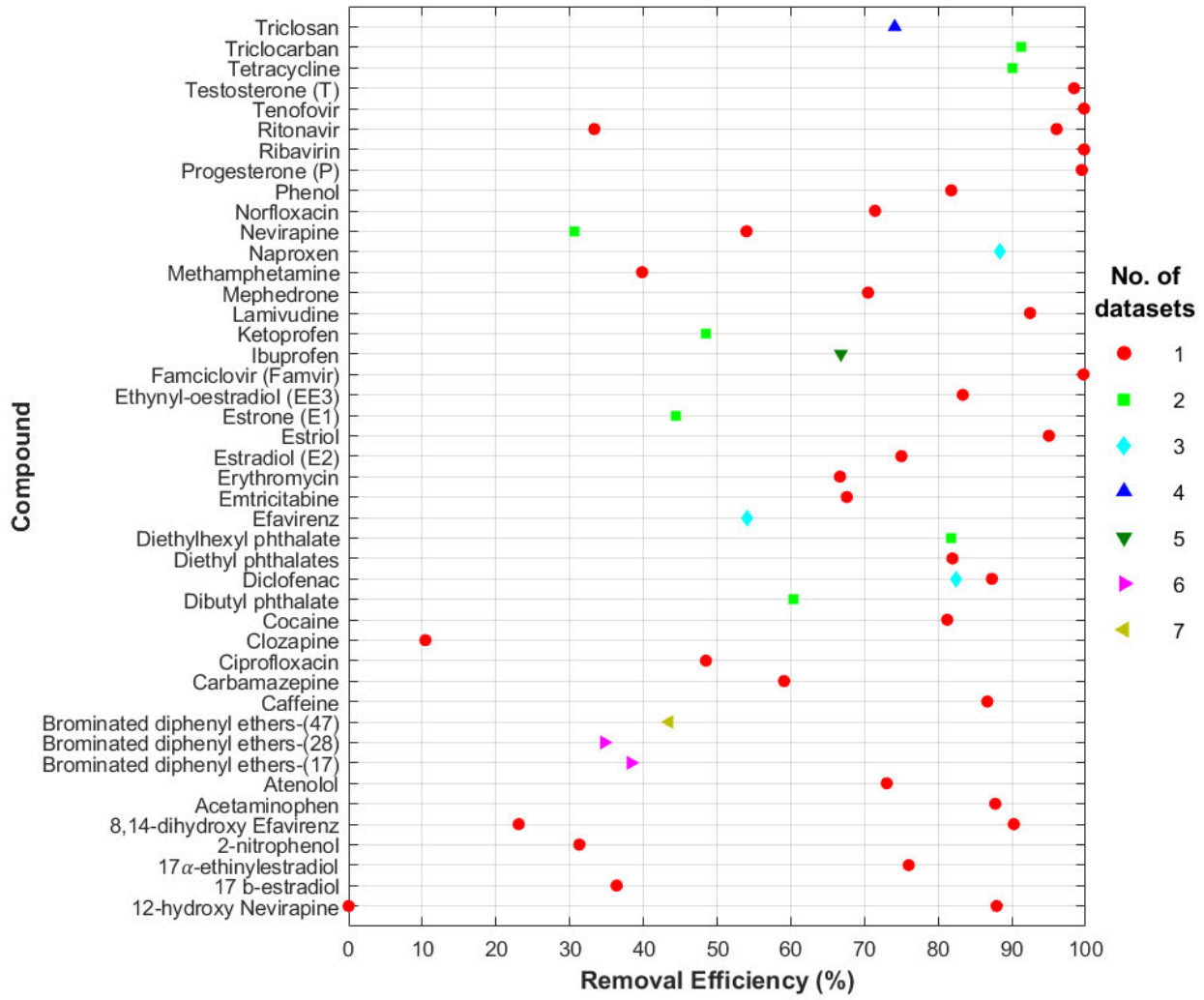


Figure 7: Percentage removal of individual emerging contaminants in WWTPs across South Africa. The removals shown here are overall removal of a compound in WWTPs, which is calculated from the reported influent and effluent concentrations in literature.

2.6 Other sources of ECs in the water environment

2.6.1 Agricultural runoff

The source of drinking water in most parts of South Africa is surface water, and the presence of ECs in surface water could be the common source/origin of ECs in drinking water. A similarity in concentration levels of herbicides in drinking water and surface water was observed, which suggests that agricultural runoff has an important contribution in transporting the herbicides from agricultural land to surface water and finally to drinking water. The herbicides, Atrazine and Terbuthylazine were detected at higher concentrations in the drinking and surface water sources of the North zone, reflecting the role of agricultural runoff for their increased levels (section 2.2). Furthermore, herbicides such as Atrazine is used more in the North zone compared to other provinces in South Africa which support their presence in surface waters in those regions. Atrazine usage across South Africa is 1015 tons per annum, of which 88% is applied to maize crop alone (Dabrowski, 2015). The highest application rate of Atrazine (0.27 – 0.50 kg/hectare) has been reported in parts of the North zone (Northwest, Gauteng and some parts of the Free State) by Dabrowski, (2015) which further supports the agricultural runoff as a reason of EC pollution in surface waters. Similarly, Terbuthylazine is also one of the commonly used herbicides in South Africa to control marigold in maize crops (Heri et al., 2008). More than 30 pesticides particularly atrazine, simazine, terbuthylazine and metolachlor are used to deal with weeds, fungi and insects in the vineyards in Western Cape (South zone) (Hildebrandt et al., 2008). These findings may suggest that increasing the domain of EC monitoring from drinking water, surface water and wastewater to agricultural runoff will significantly contribute towards source tracking and control of EC pollution in surface water in South Africa. The National Toxicity Monitoring Programme (NTMP) is designed to establish knowledge and information resources about the quality of water resources in South Africa. The focus of the monitoring programme could be further expanded to include a vast majority of ECs and matrices to establish a comprehensive knowledge base about the EC contamination in the aquatic environment of South Africa.

2.6.2 Urine diverted dry toilets.

Non-sewered sanitation technologies such as urine diverted dry toilets (UDDTs) have been identified as one of the major sources of EC pollution in South Africa. UDDTs, a means to separate human urine from faeces in the toilets, have been implemented on a pilot-scale in many parts of South Africa (Larsen *et al.*, 2013). The eThekwini municipality in the KwaZulu-Natal province has successfully installed over 80,000 UDDTs. There are only a few studies that targeted ECs from UDDTs. Bischel et al. (2015) reported the presence of 12 ECs in source-separated urine. The major ECs detected include pharmaceuticals such as Atazanavir, Atenolol, Atenolol acid, Clarithromycin, Darunavir, Diclofenac, Emtricitabine, Hydrochlorothiazide, N4 Acetyl- sulfamethoxazole, Ritonavir, SMX and Trimethoprim (TMP). The average concentration of the detected ECs ranged from micrograms 1 µg/L (Darunavir) to milligrams per litre, 2.3 mg/L (SMX), (Table 29 Appendix 2) with average TMP concentration reported was 190 µg/L. Both SMX and TMP are prescribed for antibacterial infections and as prophylaxis for long term consumption to patients with compromised immune systems such as people infected with HIV (Madhi et al., 2002). Bischel *et al*. (2015) have also confirmed the direct relation of their higher concentrations in urine with increased consumption (by 4-11% per cent) in HIV positive patients. The current practice of urine disposal in UDDTs is direct discharge into soak-away pits, and with such a high concentration of ECs, their leaching into groundwater may pose a pollution risk. Furthermore, the application of fertilisers derived from urine may lead to groundwater or surface water pollution. Therefore, fertiliser producing processes should be capable of transforming or removing the ECs from source-separated urine. In the absence of fertiliser producing facility, the collection of urine from UDDTs and its treatment with low-cost processes would be a safer option than disposal in soak-pits. Future research should be aimed at broadening the list of compounds for EC monitoring in UDDTs and their removal through various technologies.

2.6.3 Landfill leachate

Poor management strategies of the landfill leachate can lead to EC pollutions in nearby freshwater sources. Therefore, constant monitoring of landfill leachates could form one of the key elements for EC pollution control in South Africa (Nomngongo et al., 2012). However, proper disposal of the waste and treatment of landfill leachate is a growing concern in South Africa. Disposal of untreated leachate into the available sewer is a common practice (DEAT, 1999: Joubert, 1999) which could lead to increased EC loading in municipal WWTP.

Daso *et al.* (2013) confirmed landfill leachates from three landfill sites in the City of Cape Town (Western Cape Province), as a source of polybrominated diphenyl ether (PBDE) in the environment. The maximum concentration of the sum of eight PBDE congeners detected was 2.2 µg/L (Table 30 Appendix 2). It has also been reported that landfills without geomembrane are a major contributor to the occurrence of PBDEs in groundwater (Sibiya et al., 2017). Olukunle and Okonkwo (2014) also reported the occurrence of brominated flame retardants in unlined landfills in Western Cape Province (South zone). Nevertheless, the concentration reported by Olukunle and Okonkwo (2014) was in the range of pg/l. Sibiya et al. (2017) reported the occurrence of nine different PBDEs in the leachate from Gauteng province (North zone) within the range of 0.316 - 1.36 ng/L (winter) and 0.560 -1.08 ng/L (summer) and in nearby soil sediment, it was 3.00 - 4.91 ng/g (winter) and 2.50 - 3.71 ng /g (summer). The authors reported a direct relationship with the concentration of PBDEs in leachate and the receiving soil. Organophosphorus flame retardants (OPFRs) were also reported by Sibiya et al. (2019) in landfill leachates from the same city. The study concluded a higher concentration of OPFRs (52 - 14,500 ng/L) in the landfill leachates indicating their presence in South African consumer items. Similar to PBDEs, other relevant ECs of concern are also reported from the landfill leachates globally. Masoner et al. (2016) reported the presence of 101 different ECs in final landfill leachates from 22 landfill sites (16 municipal and 6 private landfills) across the United States. Consequently, even in final leachates which are the leachate disposed to the environment for disposal or treatment, the concentration of ECs ranged from 2 ng/L to seven orders in the case of bisphenol A (172 mg/L). Therefore, a high concentration of ECs in the leachate is a serious concern as it is a potential threat to the adjacent aquatic sources (Andrews et al., 2012). The first step in the regulation of EC contamination is its screening in the landfill leachates and designate possible treatment approaches. However, only a few studies have been conducted in this aspect, thus far in South Africa. The disposal of leachate into sewers does not offset the EC screening of landfill leachate. In that scenario, the screening will help to identify the increase in EC pollution loading at the WWTP which will guide up-gradation of the wastewater treatment processes for effective EC removal using advanced tertiary treatment processes.

2.7 Matrix effect

If the matrix effect percentage (%ME) of the investigated ECs is above 100 percent, then those ECs exhibit ion enhancement (Van Eeckhaut *et al.*, 2009). Whereas a value below 100 percent indicates ion suppression (Zhou *et al.*, 2017). The matrix effect refers to the phenomenon where the presence of water pollution, interference, and other ECs in a water sample can alter the response of a target EC in a chromatographic analysis. This can lead to either ion suppression or ion enhancement, which ultimately affects the accuracy of the results (Trufelli *et al*., 2011; Marshall *et al*., 1998). In various studies related to ECs in water sources, different matrix effect percentages (%ME) were observed. In a study by Mokgope *et al.* (2022) that investigated the presence of antiretroviral drugs (ARVs) in wastewater, including Nevirapine and Efavirenz, the %ME ranged from 71% to 79%. In a separate study by Sodré and Cavalcanti (2018) that focused on the occurrence of carbamazepine in water sources within the Brazilian Federal District, the %ME for carbamazepine was found to be 81%. Cardoso *et al.* (2011) conducted a study investigating the presence of atenolol and sulfamethoxazole in surface and public supply water. In this study, the %ME was reported as ≤50% for atenolol and ≥80% for sulfamethoxazole. These %ME values represent how the matrix, such as water, can influence the analysis of these pharmaceutical compounds. The variation in %ME may depend on factors like the type of water source, the analytical method used, and the specific compounds being studied.

2.8 Hazard Analysis by Critical Control Points system

The drinking water treatment plant implements Hazard Analysis Critical Control Point (HACCP) principles to guarantee the purity of the water that is distributed to the public. To ensure that water quality is safe to consume, the HACCP system is used to anticipate and avoid contamination. Critical control points (CCPs) in water treatment are the process steps that must be strictly adhered to guarantee that potable water is produced. Water treatment processes such as filtration and chemical disinfection are essential because they may remove or inactivate hazardous emerging contaminants.(Damikouka *et al*., 2007, Commission *et al.*, 2003).

To effectively implement HACCP principles, it was necessary to follow the seven steps of the HACCP system:

- Conduct a hazard analysis: This involved identifying potential hazards in the water treatment process, such as emerging contaminants.
- Determination of the critical control points (CCPs): These are the points in the process where control measures were applied to prevent, eliminate, or reduce hazards to an acceptable level.
- Establish critical limits: These are the maximum or minimum values for the CCPs that were met to ensure the safety of the water.
- Implement monitoring procedures: These are the procedures used to monitor the CCPs and ensure that critical limits are were met.
- Establish corrective actions: These are the actions that must be taken if a CCP was not under control.
- Implement verification procedures: These are the procedures that were used to confirm that the HACCP system is working effectively.
- Establish documentation and record-keeping procedures: These were the procedures used to maintain records of the HACCP system and ensure that it is being followed.

By applying these principles to water treatment at the drinking water treatment Plant, it should be possible to ensure that the water produced is safe for consumption and meets the relevant food safety standards.

2.9 An Overview of Chlorination in water bodies and its potential effects

Chlorination is a widely utilized disinfection method employed in drinking water treatment facilities (Blatchley III et al., 1997). Despite the potential advantages of alternative disinfectants in certain situations or for specific pathogens, chlorination remains a favourable choice due to its significant oxidation potential, broad-spectrum disinfection capabilities, residual effectiveness, widespread use, rapid pathogen inactivation, cost-effectiveness, and benefits such as the removal of ECs (van Dijk and Verbrugh, 2022, Mazhar et al., 2020, Clayton et al., 2021, Ramrakhiani et al., 2022). Chlorine (Cl_2) can be introduced to water either in gaseous form or in liquid bleach form of sodium hypochlorite (NaOCl) (Skinner, 2005). When chlorination occurs and the disinfectant dissolves in water, it undergoes reactions with water molecules. These reactions lead to the formation of hypochlorous acid (HOCl) and hypochlorite ions (OCl^-) (Foundation, 2023). The active disinfecting agent responsible for eliminating bacteria, ECs and viruses in water is the HOCl. It breaks down into OCl^- and hydrogen ions (H^+). The efficacy of chlorine as a disinfectant is derived from its ability to interact with microorganisms and pharmaceutical waste, disrupting their cellular structures, essential enzymes, and chemical compositions, this ultimately results in their degradation and removal (Centers for Disease Control and Prevention, 2008). In some water treatment facilities, an alternative form of chlorination known as chloramines is used instead of chlorine gas or hypochlorite (Prevention, 2022). Chloramines are formed by the reaction of chlorine with ammonia or organic nitrogen compounds. They offer improved stability and longer-lasting disinfection effects (Lenntech, 1998). Initially, monochloramine (NH_2Cl) is formed, which can further react with hypochlorous acid to generate dichloramine ($NHCl_2$) and trichloramine (NCl_3). Additionally, chlorine dioxide is also employed as a disinfectant in drinking water treatment plants (How et al., 2017). It is typically produced by reducing sodium chlorate ($NaClO_3$) using various reducing agents such as sulphur dioxide (SO_2), methanol (CH_3OH), or chloride ions (Cl^-) in sulfuric acid (H_2SO_4) solutions(Qian et al., 2007). The reaction mechanisms and dissociation processes of chlorine gas, sodium hypochlorite, chloramine, and chlorine dioxide are as follows:

Chlorine gas (Cl_2) dissolves in water and undergoes a series of reactions:

$Cl_2 + H_2O \rightleftharpoons HOCl + HCl$ (1)

$HCl + H_2O \rightleftharpoons H_3O^+ + Cl^-$ (2)

HOCl can further dissociate to:

$HOCl \rightleftharpoons H^+ + OCl^-$

Sodium Hypochlorite (NaOCl), commonly known as liquid bleach, dissociates in water:

$NaOCl \rightleftharpoons Na^+ + OCl^-$ (3)

Chloramine is formed by the reaction of chlorine with ammonia or organic nitrogen compounds:

$NH_3 + HOCl \rightleftharpoons NH_2Cl + H_2O$ (4)

$NH_2Cl + HOCl \rightleftharpoons NHCl_2 + H_2O$ (5)

$NHCl_2 + HOCl \rightleftharpoons NCl_3 + H_2O$ (6)

2.9.1 Factors Affecting the Chlorination Process in Drinking Water

The chlorination process in drinking water can be influenced by several factors. Here are the factors that can affect the process of chlorination:

- The chlorine dosage: The quantity of chlorine added to the water has a direct impact on its disinfection effectiveness. Higher levels of chlorine can improve pathogen removal, but excessive amounts can lead to taste and odour issues and the formation of DBPs (Safe Drinking Water Foundation, 2023).

- Temperature: The temperature of the water plays a significant role in the efficiency of chlorination. Generally, warmer water requires less chlorine for disinfection compared to colder water. However, higher temperatures can promote the formation of DBPs (Safe Drinking Water Foundation, 2023).

- The pH Level: The pH of the water is a critical factor in the efficacy of chlorination. The disinfection effectiveness of chlorine is influenced by the water's pH, as chlorine exists in different forms depending on the pH. Each form of chlorine exhibits varying disinfection capabilities. The recommended pH range for optimal chlorination effectiveness is typically between 6.5 and 7.5 (Centers for Disease Control and Prevention, 2020).

- Total Dissolved Solids (TDS): TDS in water can significantly slow down the chlorination process, necessitating the addition of extra chlorine for successful disinfection. This is due to several factors, including increased chlorine demand, reduced chlorine residual, the formation of disinfection by-products (DBPs), and complex treatment requirements. High TDS levels lead to increased chlorine demand, as TDS contains dissolved substances such as minerals and organic matter that react with chlorine. This results in a decrease in chlorine residual, making it less effective at disinfection. Additionally, higher TDS levels can intensify the formation of DBPs, posing health risks. Therefore, regulated chlorine dosing is necessary to minimize their formation (Kim *et al.,* 2003).

- Conductivity: Conductivity refers to the water's ability to conduct an electric current and can be influenced by dissolved salts and ions. High conductivity levels may indicate the presence of dissolved solids that can potentially impact the chlorination process. High-conductivity water can promote corrosion in pipes and equipment used in the chlorination process and contribute to scaling, where minerals precipitate out of the water and accumulate on surfaces. Lastly, high conductivity also indicates potential interference with the chlorination process, potentially causing reduced efficiency, byproduct formation, and equipment issues (Levlin, 2010, Reader, 2023).

- Water Properties: The characteristics of water, such as turbidity (cloudiness), organic matter content, and the presence of other contaminants, can affect chlorination efficiency. Increased turbidity or higher organic matter levels can diminish chlorine's disinfection capacity and contribute to DBP formation (Lindmark *et al*., 2022; Mazhar *et al*., 2020).

- Contact Time: The duration of contact between chlorine and water is crucial for successful disinfection. Sufficient contact time allows chlorine to effectively react with pathogens and deactivate them. In situations where water contains elevated contaminant levels or maintaining an adequate chlorine residual is challenging, longer contact times may be necessary (Safe Drinking Water Foundation, 2023).

2.9.2 Effect of external factors on chlorination and disinfection by-product formation

Environmental factors have a substantial influence on both chlorination and the formation of DBPs during water treatment. Various variables, such as water quality, chlorine dosage, contact time, chlorine species, prior oxidation and pre-treatment, reaction time, distribution system, and control measures, play crucial roles (Kim et al., 2015). Prior oxidation and pre-treatment are crucial steps in water treatment to reduce the initial concentration of ECs. Longer reaction times within treatment processes allow for more thorough ECs removal, especially for persistent compounds (Tijani et al., 2014). The distribution system, which transports treated water to consumers, can also harbor ECs, posing public health risks. Proper maintenance and material selection, as well as strategies to reduce water residence time within the network, are essential (Ouda et al., 2021). Implementing control measures involves monitoring, adjusting treatment processes, optimizing distribution system design, and implementing source water protection measures to manage and minimize ECs at various stages of water treatment and distribution (Xie et al., 2023). These external parameters can also affect the type and magnitude of DBP formation during the chlorination process.

2.9.3 Chlorine reactivity towards endocrine disruptors, inorganic, organic micro pollutants, and other emerging contaminants relevant to water treatment

It is widely acknowledged that chlorine reacts with various functional groups in a decreasing sequence; phenolic group, tertiary ammonium ions, carbon-carbon double bonds, aromatic compounds, carbonyl compounds, and amides are less reactive than primary, secondary amines and thioethers (Tundo, *et al.* 2018). Due to chlorine's less reactivity with other functional groups like alkyl, hydroxy, amide, and carboxylic acid, it is expected that most of the reactions with nonylphenol, bisphenol A, triclosan, and their chlorinated derivatives, estrogenic steroid hormones, and acetaminophen will mostly happen on the phenolic ring (Deborde and Von Gunten 2008). The initial electrophilic attack by chlorine on these compounds is anticipated to occur at the ortho or para position of the phenolic group. While the identification of mono-, di-, and tri-chlorinated transformation products of these chemicals provides evidence of their reactivity (Hu *et al*. 2002; Postigo *et al*. 2021). In the case of inorganic compounds, ammonia, halides (Br^- and I^-), $SO3^{2-}$, CN^-, NO^{2-}, As (III), and Fe (II) are known to react rapidly with HOCl, while inversely reacting slowly with Mn (II) in homogeneous systems (Deborde and Von Gunten 2008). Chlorination reactivity can vary between functional groups, for instance, the cyclopropylethynyl group is highly strained and electron-deficient, making it highly reactive towards electrophiles such as chlorine (Chen *et al.* 2002). While methyl groups are generally inert, they can still undergo chlorination with strong enough oxidants (Postigo and Richardson 2014). Secondary alcohols can be oxidized to ketones, which are more reactive towards chlorination, and while the reactivity of alkyl substituents towards chlorination depends on the nature of the alkyl group and reaction conditions (Cherney *et al*. 2006). Nitrogen atoms present in the amide group and pyridine ring can activate adjacent carbon atoms towards chlorination (Linge *et al*. 2020), which is similar to the heterocyclic oxygen atom found in the benzoxazine group (Nihemaiti *et al.* 2017). Lastly, the highly polarized carbon atom present in both the carbonyl and imine groups makes them vulnerable to electrophilic attack (Mcdowell *et al.* 2005), while the highly electronegative sulphur atom in the sulfonamide group makes it relatively resistant to chlorination, except under conditions of high temperatures and strong oxidants (Qiang *et al*. 2006). These functional groups can significantly affect the reactivity and pharmacological properties of the ECs in their interaction with chlorination.

Chlorination is known to readily react with functional groups present in various environmentally relevant ECs. For instance, sulfamethoxazole and efavirenz, two commonly encountered ECs, contain several readily reactive functional groups such as cyclopropyl ethyl, sulfonamide ($-SO_2NH_2$), and benzoxazine groups. Similarly, atenolol, another EC, possesses readily reactive functional groups, including a secondary alcohol group (-OH) and an alkyl substituent ($-CH_2CH_2OH$) (Albini and Fasani, 2004). Below Figure 8 is an illustration of the hypochlorous acid reaction: amine and sulfur functional group.

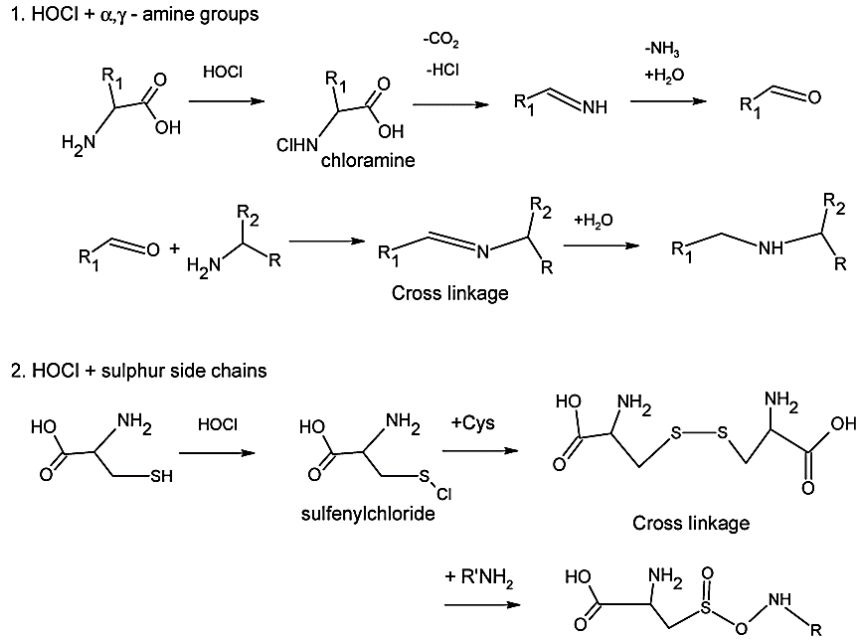


Figure 8:Hypochlorous Acid Reaction: Amine and Sulfur Functional Groups (Kerkaert et al., 2011)

In the case of Nevirapine, an EC used in pharmaceuticals, it exhibits readily reactive functional groups such as an amide ($-CONH_2$) group and a pyridine ring (Kang *et al.*, 2016). Lastly, carbamazepine, a widely studied EC, contains several readily reactive functional groups like carbonyl and imine (-C=N-) groups (Bruckner, 2001; Mcdowell *et al*., 2005; Kalgutkar *et al*., 2010; Program, 2017; Mthiyane, 2022; Khan Academy, 2023). When subjected to chlorination, these functional groups may undergo reactions leading to the formation of chlorinated by-products. The reactions and mechanisms are diagrammatically illustrated in Figure 9 below, which represents the removal route of the selected and investigated ECs in this study. The following alphabets (A, B, C, D, and E) are used to denote the specific ECs: nevirapine, atenolol, carbamazepine, sulfamethoxazole, and efavirenz, respectively.

When these ECs are subjected to degradation or removal through chlorination, they undergo a series of reactions, including chlorination, hydrolysis, and oxidation, ultimately leading to the formation of chlorinated by-products. In the initial chlorination reaction, chlorine gas (Cl_2) replaces hydrogen atoms within the chemical structure of (A, B, C, D, and E), resulting in the formation of chlorinated derivatives of these compounds (Altarawneh *et al*. 2009). This process also produces hydrochloric acid (HCl) as a by-product (Motupally *et al*., 1998). During the hydrolysis reaction, the chlorinated derivatives formed earlier can undergo hydrolysis when they intearact with water (H_2O), leading to the degradation of the ECs (Quintana *et al.* 2014; De Laat and Stefan 2018). Additionally, the residual chlorine further oxidizes (A, B, C, D, and E) and their degradation products into smaller molecules, resulting in oxidized products (Huang *et al.* 1993; Westerhoff *et al.* 2005). It's important to note that chlorination can also give rise to the formation of chlorinated by-products, including trihalomethanes and haloacetic acids (Bletsou *et al.* 2015), etc. These by-products result from various reactions involving A, B, C, D, and E, their degradation products, and chlorine (Santos *et al.* 2012).

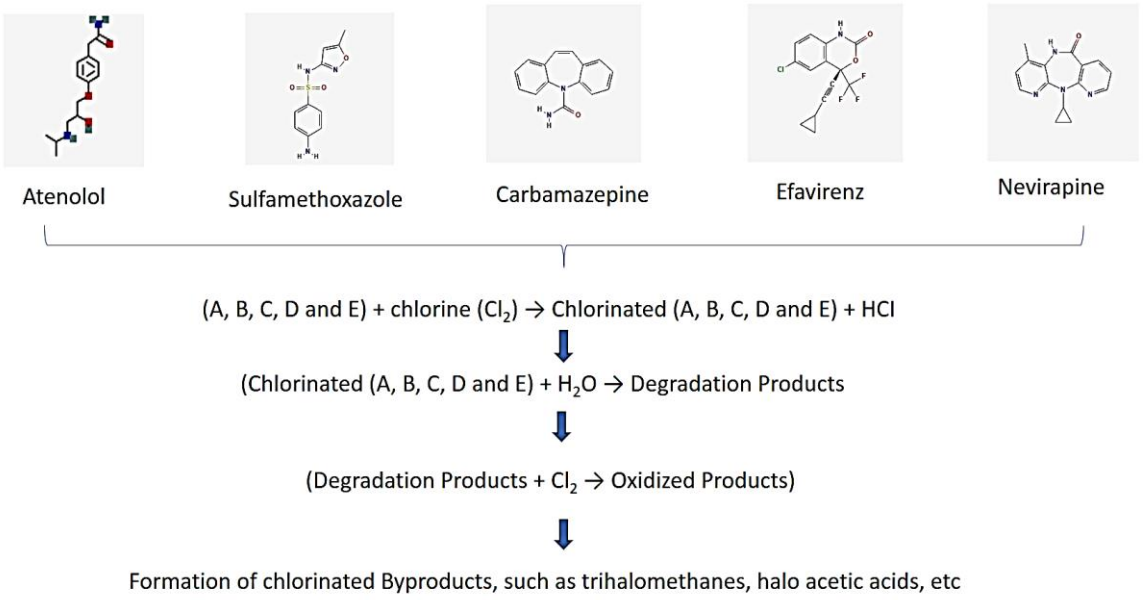


Figure 9: The removal and degradation route of the selected and investigated ECs by chlorination in drinking water.

2.9.3.1 Reaction kinetics between ARVs and chlorine

Chlorination reactions with chemicals follow pseudo second order kinetics and first order kinetics respectively (Lee and Gunten, 2009). Therefore, the objective of the study was to obtain the pseudo second order rate constant (K_{app}) and the first order rate constant (K_{obs}). Both K_{app} and K_{obs} depend on the pH (Acero *et al*., 2010). The rate of change of concentration of ARVs $\frac{d[A]}{dt}$ during chlorination can be explained according to equation (E.q.7). Under slow reaction kinetics and high chlorine concentration [Cl_2] compared to the concentration of antiretroviral drug [A] at time t, equation (E.q.7) can be explained as equation (E.q.8).

$$\frac{d[A]}{dt} = K_{app}[A][Cl_2] \qquad (7)$$

$$\frac{d[A]}{dt} = K_{obs}[A] \ \ for\ [Cl_2] \gg [A] \qquad (8)$$

$$Where, K_{obs} = K_{app}[Cl_2] \qquad (9)$$

Where [Cl_2] is the total concentration of the chlorine, which equals the sum of chlorine ions (HOCl and OCl). [A] Is the concentration of the ARV at any time (t). Studies have found ARV concentrations in surface water sources in the nanograms per litre range (Wood *et al.*, 2015). Surface water is generally the raw water source for a majority of the drinking water treatment plants across the globe. Therefore, the objective of the experiments was to determine the degradation of ARVs under slow order reaction kinetics with [Cl_2]>> [A]. The model to obtain pseudo second order rate constant (K_{app}) starts with equation (8) that can be described by equation (E.q.10) and a plot of $\ln\frac{[A_0]}{[A]}$ versus time gives a straight line for the slope was K_{obs}. Different experiments at various pH and temperatures were performed, as explained in the methods section, to obtain K_{obs} after linear regression. For experiments performed with different initial concentrations of chlorine, the slope of the plot of $\frac{\ln[A_0]}{[A]}$ versus chlorine concentration after linear regression estimated K_{app} values. For experiments performed at different pH, temperature, and initial concentration of ARVs, the K_{app} value was obtained from K_{obs} by dividing it with the initial concentration of chlorine according to equation ((E.q.11).

$$ln\frac{[A_0]}{[A_t]} = K_{obs}\text{t} \quad (10)$$

$$K_{app} = \frac{K_{obs}}{initial\ Cl_2} = \frac{K_{obs}}{[\ Cl_2]} \quad (11)$$

2.9.2 Formation of disinfection by-products and their health risks

Disinfection by-products (DBPs) are formed as a result of the reaction between disinfectants and substances present in drinking water (Barrett *et al*., 2000). Among the common DBPs are trihalomethanes (THMs), haloacetic acids (HAAs) and Haloacetonitriles (HANs) (Righi *et al*., 2014). DBPs, including various trihalomethanes (such as chloroform, bromodichloromethane, dibromomethane, and bromoform), haloacetic acids (such as monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, and bromochloroacetic acid), and haloacetonitriles (such as trichloroacetonitrile (TCAN), dichloroacetonitrile (DCAN), and bromochloroacetonitrile (BCAN), are commonly found in water treatment systems. These DBPs are formed through chemical reactions that occur when chlorine reacts with naturally occurring organic compounds like humic and fulvic acids. (Liang and Singer, 2003, Richardson, 2003). During these reactions, chlorine atoms are replaced by bromine, iodide and other halogen atoms, resulting in the formation of disinfection by-products (Hanson and Solomon, 2004, Cohl et al., 2015, Li and Mitch, 2018).The United States Environmental Protection Agency (EPA) has established maximum contamination limits (MCLs) for total trihalomethanes (THMs) in drinking water. The MCL for total THMs is set at 80 parts per billion (US EPA, 2017). Additionally, individual concentration limits have been specified for each of the four categories of THMs: bromodichloromethane (60 µg/L), dibromochloromethane (60 µg/L), bromoform (80 µg/L), and chloroform (70 µg/L) (US EPA, 2017). When the MCL for haloacetic acids and haloacetonitriles, specifically > 0.060 mg/L, it is considered a health hazard due to an increased risk of cancer (Contaminants, 2012). Table 3 summarizes the data obtained from various sources regarding the occurrence of THMs and HAAs in drinking water.

Table 3: Disinfection by-products through chlorination processes

DBPs	Cl_2 (mg/L)	pH	Time	Temperature (°C)	formation (µg/l)	Reference
Trihalomethanes						
chloroform	1	7	160 min	20	50.01	(Li *et al.* 2019)
bromodichloromethane	1	7	160 min	20	8.49	(Li *et al.* 2019)
dibromochloromethane	1	7	160 min	20	3.31	(Li *et al.* 2019)
chloroform	1.5	7	7 hrs	20	8.85	(Dong *et al.* 2020)
dibromochloromethane	1.5	7	7 hrs	20	1.83	(Dong *et al.* 2020)
bromoform	1.5	7	7 hrs	20	0.72	(Dong *et al.* 2020)
Halo acetic acids						
monochloroacetic acid	0.7	7.4	6 hrs	20	6.1	(Dong *et al.* 2019)
monobromoacetic acid	0.7	7.4	6 hrs	20	1.07	(Dong *et al.* 2019)
dichloroacetic acid	0.7	7.4	6 hrs	20	0.22	(Dong *et al.* 2019)
dichlorobromoacetic acid	0.7	7.4	6 hrs	20	4.04	(Dong *et al.* 2019)
Haloacetonitriles						
Trichloroacetonitrile	1.5	7	7 hrs	20	0.88	(Dong *et al.* 2020)
Dichloroacetonitrile	1.5	7	3 hrs	20	0.17	(Dong *et al.* 2020)
Bromochloroacetonitrile	1.5	7	5 hrs	20	0.28	(Dong *et al.* 2020)

The presence of DBPs has the potential to affect both the environment and human health (Zhang et al., 2016). The release of treated water that contains DBPs into the environment can have negative impacts on aquatic ecosystems and may also pose health risks to humans, such as stunted growth, decreased reproductive capabilities, abnormal development, and impaired behaviour (Cui et al., 2021). The presence of these substances in the food chain can result in their accumulation, which may cause bioaccumulation and bio-magnification (Bienfang et al., 2013). DBPs can enter the human body through various means such as ingestion, inhalation, and dermal contact(Richardson, 2005). Studies have shown that prolonged exposure to DBPs can lead to negative health outcomes such as an elevated risk of specific cancers, reproductive complications, and cardiovascular problems (Kar and Senthilkumaran, 2020, Li and Mitch, 2018, Costet et al., 2011). The objective of regulations and water treatment practices is to reduce the formation of DBPs and ensure that their levels remain within allowed limits (Werschkun et al., 2012). The implementation of advanced treatment techniques, including alternative disinfection methods and improved filtration processes, are also aimed at reducing the levels of DBPs in treated water (Fetyan and Salem Attia, 2020). The presence of DBP in the environment is a critical issue that requires monitoring and assessment to comprehend its potential impacts and implement suitable mitigation strategies (Drakvik et al., 2020).

2.9.3 Evaluating the Potential of Advanced Oxidation Processes versus Chlorination for Enhanced Water Disinfection and Emerging Contaminant Removal

Advanced oxidation processes (AOPs) are chemical treatment methods that employ highly reactive hydroxyl radicals to oxidize and break down both organic and inorganic contaminants present in water. These AOPs have the capability to efficiently degrading and removing various harmful substances, such as microorganisms and ECs in drinking water, while reducing the formation of DBPs (Parsons, 2004, Khajouei et al., 2022, Ganiyu et al., 2015). For instance, the use of UV radiation in conjunction with chlorine (UV/Cl_2), as well as the addition of ammonia (chloramination) at specific Cl/N ratios, can generate effective disinfectants, although less potent than chlorination (Fast et al., 2017, Zhu et al., 2018). UV/Cl and chloramination processes have the advantage of generating fewer disinfection by-products when compared to traditional chlorination methods (Chen *et al.*, 2021, Ike *et al.*, 2019).

Additionally, these AOPs exhibit the ability to degrade a wider range of contaminants through oxidation reactions, thereby enhancing the overall effectiveness of water treatment (Farzanehsa et al., 2023). However, it is important to consider that UV/Cl and chloramination processes may acquire higher operational costs than typical chlorination due to their energy requirements and the need for ammonia addition (Zhao et al., 2022). In the UV/Cl_2 process, using the cyclopropylethynyl functional group found in ECs such as Efavirenz, a chlorine reaction occurs following a sequential radical chain reaction. Radical chain reaction process step by step. First, by applying heat or UV light, chlorine (Cl_2) undergoes homolytic cleavage, forming two chlorine radicals (Cl•). During the propagation stage, the chlorine radical (Cl•) reacts with cyclopropylethynyl (C_5H_4), resulting in the formation of a cyclopropylethynyl radical ($C_5H_4^{\bullet}$) (LibreTexts, 2019, LibretextsChemistry, 2019, De Laat and Stefan, 2017).This cyclopropylethynyl radical (C_5H_4) can further react with another chlorine molecule (Cl_2), producing cyclopropylidene chloride (C_5H_3Cl) and regenerating the chlorine radical (Matyjaszewski et al., 2006, Morgan, 1930). The propagation steps continue as the cyclopropylidene chloride radical (C_5H_3Cl) reacts with Cl_2, generating cyclopropylidene dichloride ($C_5H_3Cl_2$) and another chlorine radical (Severin et al., 2006, Wojnárovits and Takács, 2021).These steps can repeat, leading to more cyclopropylidene dichloride and chlorine radicals. Finally, the termination step takes place, where two radical species combine, forming non-radical products and stopping the chain reaction (De Laat and Stefan, 2017, Stefan, 2017). Various termination steps are possible, with one example being the reaction between a cyclopropylidene chloride radical (C_5H_3Cl) and a chlorine radical (Cl•), resulting in cyclopropylidene dichloride ($C_5H_3Cl_2$) (Feng et al., 2007, Guo et al., 2022). Understanding this step-by-step flow provides insights into the UV/Cl process and its reaction mechanism involving cyclopropylethynyl. The summary of the reaction mechanisms of the initial, propagation and termination stage (Walling, 1957, McBee *et al*., 1942, Pease and Walz, 1931, Kharasch *et al*., 1941) are as follows:

$Cl_2 \rightarrow 2Cl\bullet$

$C_5H_4 + Cl\bullet \rightarrow C_5H_4{\cdot}Cl$

$C_5H_4{\cdot} + Cl_2 \rightarrow C_5H_3Cl + Cl\bullet$

$C_5H_3Cl{\cdot} + Cl_2 \rightarrow C_5H_3Cl_2 + Cl\bullet$

Table 4 below summarizes the available data obtained from various sources about the effectiveness of UV/Cl_2 and chlorination in removing endocrine disruptors and pharmaceutical ECs from water bodies in comparison to chlorination. According to the findings, chlorination disinfection appears to have a significantly higher removal effect compared to UV/Cl_2 and chloramination. However, the high removal efficiency of chlorination is accompanied by a higher strength of chlorine, which can result in the formation of high DBPs in drinking water. Prolonged exposure to high levels of DBPs may lead to potential health complications in the long run. On the other hand, UV/Cl_2 and chloramination processes offer a promising approach to mitigating DBP formation. These methods can effectively reduce DBPs and their associated health risks.

However, it is important to note that implementing UV/Cl_2 and chloramination processes on a large production scale may not be feasible in the long term, particularly in low- gross domestic product GDP revenue countries. Factors such as operational costs, energy requirements, and the need for precise control of ammonia and chlorine doses make these processes less viable for long-term implementation in such regions.

Table 4: Efficiency of Emerging Contaminant Removal: A Comparison of Chlorination and Advanced Oxidation Processes

Pharmaceutical type	ECs	CL_2 (mg/L)	(Cl/N) ratio	UV/CL_2	pH	Time	Decay period	Temperature (°C)	Removal	Reference
Antibiotics	tetracyclines	1.2			-	24 hr	-	25	>99%	(Gibs *et al.* 2007)
	trimethoprim	1.2			-	24 hr	-	25	42%-99%	(Gibs *et al.* 2007)
	sulfonamides	1.2			-	24 hr	-	25	50%–80%	(Gibs *et al.* 2007)
	fluoroquinolones	1.2			-	24 hr	-	25	30%–40%	(Gibs *et al.* 2007)
	erythromycin	3.5–3.8			-	24 hr	-	25	90%-99%	(Gibs *et al.* 2007)
	macrolide	1.2			-	24 hr	-	25	10%	(Gibs *et al.* 2007)
	sulfamethoxazole	3.5–3.8			-	24 hr	-	25	90%-99%	(Westerhoff *et al.* 2005)
		1			-	40 min	-	20	73.08%	(Xu *et al.* 2022)
				6.67 kWh/10^3L and 42.6 mg/L of Cl_2	9				77.40%	(Ngumba, *et al* 2020)
	sulfadiazine	1.3			7.4	24 hr	-	25	73.00%	(Dong *et al.* 2019)
	fleroxacin	0.3, 0.7, 1.0, and 1.3			7.4	60 min	-	20	28%, 32%, 44%, and 48%	(He *et al.* 2019)
Beta-blocker										

	atenolol	1			-	-	60 days	25	51% to 95%	(AstraZeneca 2016)
Anti-eliptic										
	Carbamazepine	1.32			-	1 hr	-	25	44.4%-99%	(Capodaglio *et al.* 2018).
			1.6		5.5	30 min	-	25	72.40%	(Wang *et al.* 2018)
			1.6		9.5	60 min	-	25	72.40%	(Wang *et al.* 2018)
Hormone										
	17b-estradiol	0.5			7.2	10 min	-	25	99%	(Li *et al*. 2017)
	Estriol	0.3 to 1.3			7	60 min	-	25	47.6% to 73.4%	(Dong *et al.* 2020)
Antiretroviral drugs										
	Lamivudine			6.67 kWh/10^3L and 42.6 mg/L of Cl_2	9				77.40%	(Ngumba, *et al* 2020)
	Nevirapine			6.67 kWh/10^3L and 42.6 mg/L of Cl_3	9				20.80%	(Ngumba, *et al* 2020)
		11.51			8	24	-	20	>90%	(Wood *et al.* 2016)

2.10 Literature review conclusions and future research directions

A critical review of EC pollution in aquatic sources of South Africa, their removal in WWTPs, followed by a risk assessment was carried out in the current review. The EC contamination challenges in South Africa cannot be generalised and can be stratified among different communities due to the diverse living standards prevailing in the country. The prolonged exposure of EC contaminations on the population which is dependent on surface water can be assessed by investigating the EC levels in the local water source and the level of consumption by human beings. A survey-based study can be useful to investigate the source of water and its estimated consumption. Furthermore, the use of surface water for agricultural purposes may expose humans to a significant EC risk as the water is not purified by any standards. Future research can be directed towards risk assessment and developing cheaper and affordable solutions to reduce/mitigate the EC exposure risks. The conclusions from the review can be summarised as:

- Based on the literature, it is apparent that EC related research in South Africa is significantly lower than many other countries, highlighting the need for prioritising national research efforts in this direction.
- The EC concentration in urine from the UDDTs is up to mg/L range, which advocates that EC monitoring plans should include decentralised technologies.
- Analysis of data showed that the inferences about occurrence levels and sources of EC pollution in South Africa could not be derivative of developed countries. Poor sanitation, the common use and mismanagement of pit latrines, use of urine diverted toilets, and inadequate functioning of WWTPs are common issues in South Africa which may result in the increased discharge of ECs through untreated waste in surface water sources. Many peri-urban or rural communities have little access to proper sanitation services. The practice of dumping of ‘night-soil' into streets, storm drainage or directly into surface waters may be the common sources of ECs in the environment. This indicates that contemplation of WWTPs being the only source of ECs may not be adequate in South Africa. Rather, contextualisation is necessary due to different sanitation and waste handling infrastructure.

- Phthalates (DEP, DBP, BBP and DEHP) are present in the highest concentration in untreated wastewater, even up to the maximum concentration of 6.6 mg/L (DEP). Owing to their wide application, WWTPs should be monitored for these compounds and along with improving their removal in WWTP, control at source should be implemented.
- Assessment of RQ and concentration of ECs present in surface water indicated that toxicity criteria should be combined with concentration criteria, to decide priority compounds for monitoring and regulations in surface water. RQ of only twelve compounds out of thirty-two compounds was lower than 1.

Chapter 3: Emerging Contaminants: Occurrence, Analysis, and Removal Efficacies in Various Treatment Units

3.1. Introduction

Emerging contaminants (ECs) are naturally occurring or synthetic pollutants that can enter the environment through sewage and wastewater discharge, landfill leachates, direct disposal of unused drugs, and agricultural runoff (Gani et al., 2021). It is therefore important to study the sources and pathways of pharmaceutical ECs in the environment and to develop effective strategies for their removal. ECs are highly prevalent in the surface and drinking water matrices of countries, particularly in metropolitan and rural areas that have low gross domestic product (GDP) revenues and poor health services, resulting in poor wastewater treatment infrastructure (Edokpayi *et al*., 2017). The presence and long exposure of these ECs in the environment can lead to the development of drug resistance among ECs, which can lead to a range of health issues for humans and aquatic life (Gani *et al.*, 2021). On a social aspect, education and awareness campaigns can be used to encourage proper disposal of pharmaceutical ECs in order to reduce their presence in the environment (Samal *et al.*, 2022). On a technical aspect, since monitoring of ECs in drinking water is an understudied area, due to the limitation such as their low measured concentrations (which range in the µg/L-ng/L), the requirement of highly sensitive, specialized analytical instruments and analytes pre-concentration methods like solid-phase extraction (SPE) (Cimetiere *et al*. 2013). Hyphenated techniques such as fluorescence spectroscopy, biosensors, and mass spectrometry-based imaging (MSI) (Löffler and Ternes, 2003); (Isobe *et al.*, 2011, Sánchez-González *et al.*, 2016) have also been used for detection in drinking water. Analytical methods, such as gas chromatography–mass spectrometry (GC–MS), liquid chromatography–mass spectrometry (LC–MS), and liquid chromatography–tandem mass spectrometry (LC–MS/MS) are been employed for detection of various type of pollutants in drinking water (Hirsch *et al.*, 1999, Löffler and Ternes, 2003, Labadie and Hill, 2007) . A preliminary literature review conducted as part of this study revealed a lack of information regarding the presence and geographical distribution of ECs in South African aquatic environments, including surface water and drinking water treatment plants.

There have also been a few studies that have demonstrated their presence at higher levels in surface waters, including dams and rivers, which serve as sources for drinking water treatment plants. Therefore, based on the survey results, five predominant pharmaceutical ECs were selected for this study in order to evaluate their occurrence and removal from three water treatment plants in KwaZulu-Natal (KZN). A total of five key ECs were assessed for their presence and removal during various treatment stages such as coagulation, sedimentation, sand filtration, and chlorination in selected drinking water treatments, including Nevirapine (NVP) and Efavirenz (EFV), Sulfamethoxazole (SMXZ), Atenolol (ATN), and Carbamazepine (CBZ).

3.2. Materials and methods

3.2.1 Analytical standards and chemical reagents

Sulfamethoxazole (98%), Nevirapine (≥98%), Carbamazepine (97%), Atenolol (98%), Efavirenz (98%), uHPLC grade methanol (MeOH) (≥99.9%), uHPLC grade water (≥99.9%), acetonitrile (ACN) (≥99.9%), and formic acid (99.7%), ammonium acetate (98%), Supelco Hydrophilic-Lipophilic-Balanced (HLB) 200 mg/6 ml cartridge, were purchased from Sigma-Aldrich (Steinheim, Germany). The Pocket Colorimeter II Colorimeter Test Kit for Total Chlorine Analysis was purchased at HACH in South Africa and the YSI 556 multi-parameter instrument was purchased from EXO monitoring and control laboratories (PTY) LTD.

3.2.2 Drinking water treatment plant sampling sites

The collected samples consist of surface water effluent from the Nagle dam, Inanda dam, and Midmar dam. The Nagle dam effluent feeds into DWTP-1, the Inanda dam effluent feeds DWTP-2, and the Midmar dam effluent feeds into DWTP-3. The sampling sites are visually represented in Figure 10. These samples were specifically collected from DWTP units that include coagulation, sedimentation, sand filtration, and chlorination. The sampling points within each DWTP are displayed in Figure 11 for DTWP 1, Figure 12 for DTWP 2, and Figure 13 for DTWP 3.

Monthly collection of these samples occurred from August to October 2022, using 2-litre pre-cleaned Schott bottles. All sampling sites are located northwest of Durban, in the province of Kwa-Zulu Natal, South Africa. On-site tests were conducted on the collected samples using the Pocket Colorimeter II Colorimeter Test Kit for Total Chlorine Analysis and the YSI 556 multi-parameter instrument. These tests encompassed the analysis of various parameters such as pH, chlorine (Cl_2) content, total dissolved solids (TDS) %, dissolved oxygen (DO) %, salinity, conductivity (µS/cm), and temperature (°C). The results of these tests are presented in detail in Table 18 Appendix 2. Subsequently, the samples were transported to the laboratory in cooler bags and underwent filtration using a 0.22µm nylon filter. For samples collected from chlorination treatment units in each selected DWTP, ascorbic acid was added to neutralize the residual chlorine. Following filtration, the pH of the samples was adjusted to 3. Finally, the samples were stored in the refrigerator at 4 °C. The investigated ECs (Nevirapine and Efavirenz, Sulfamethoxazole, Atenolol, and Carbamazepine) molecular structures and dissociation constants (pKa) are tabulated in Table 5.

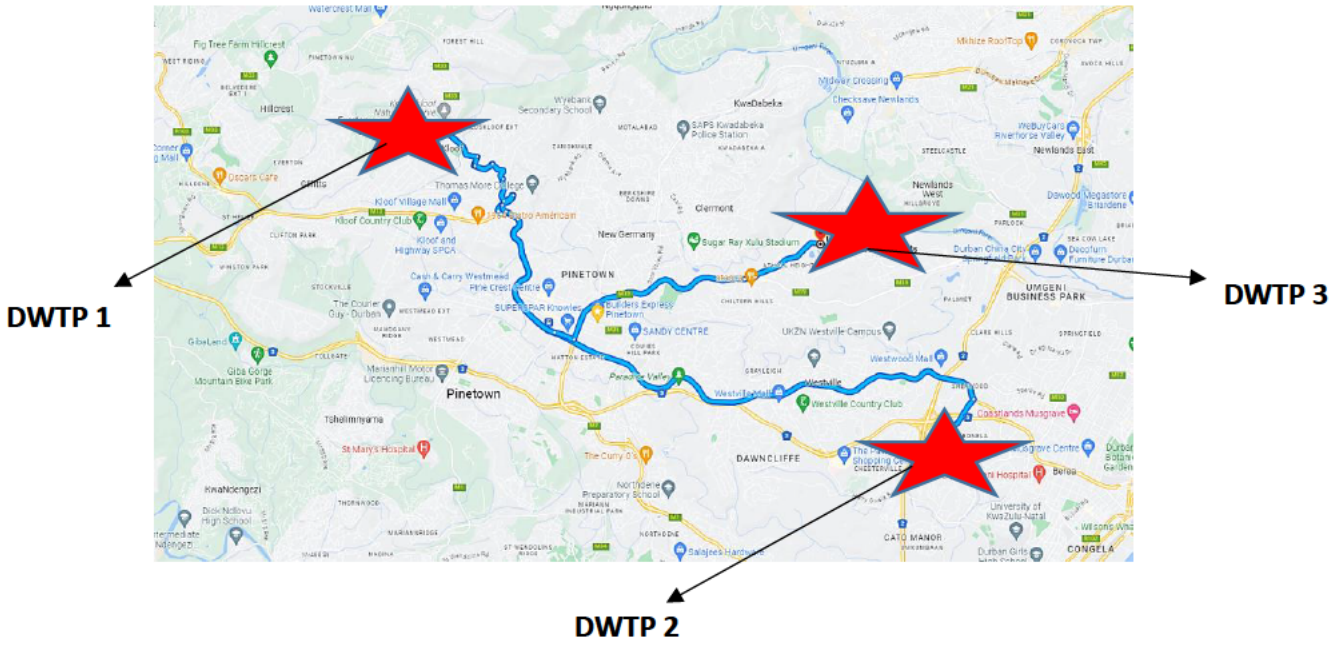


Figure 10: Map of the selected drinking water treatment plant sampling site located in Kwa-Zulu Natal, South Africa

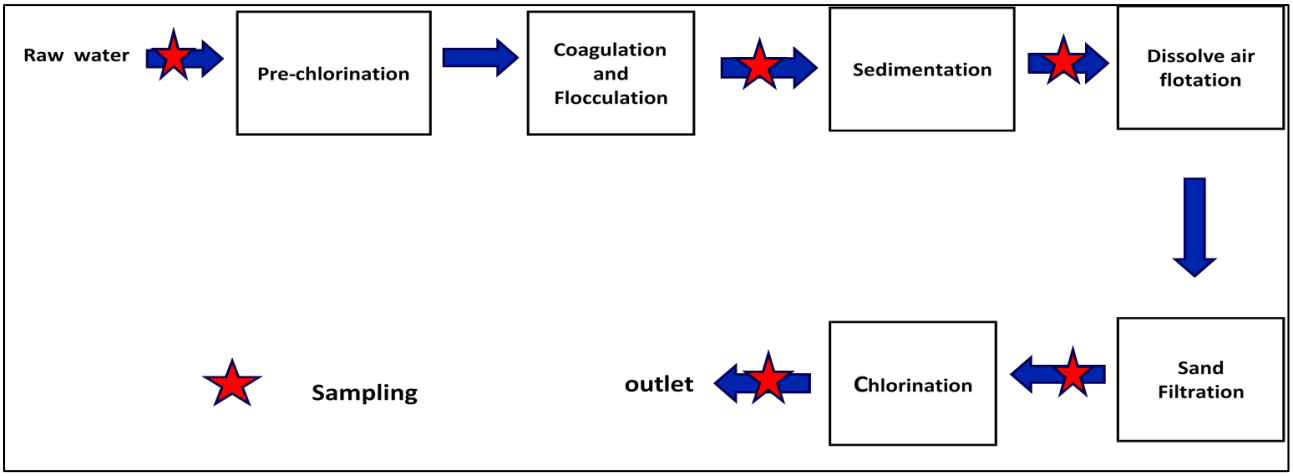


Figure 11: Depiction of Drinking Water Treatment Plant -1 Sampling Points

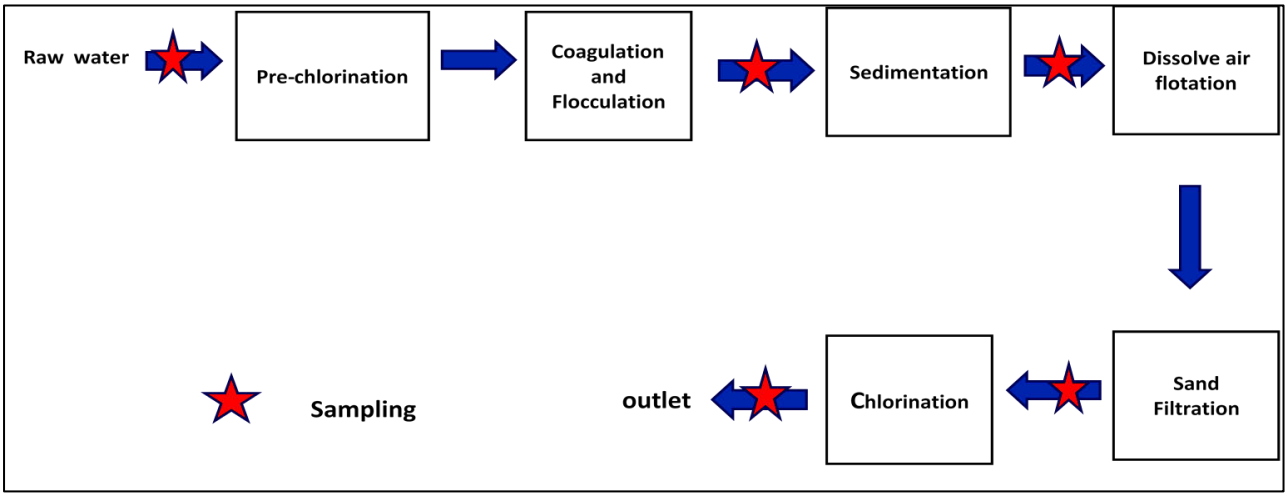


Figure 12: Depiction of Drinking Water Treatment Plant -2 Sampling Points

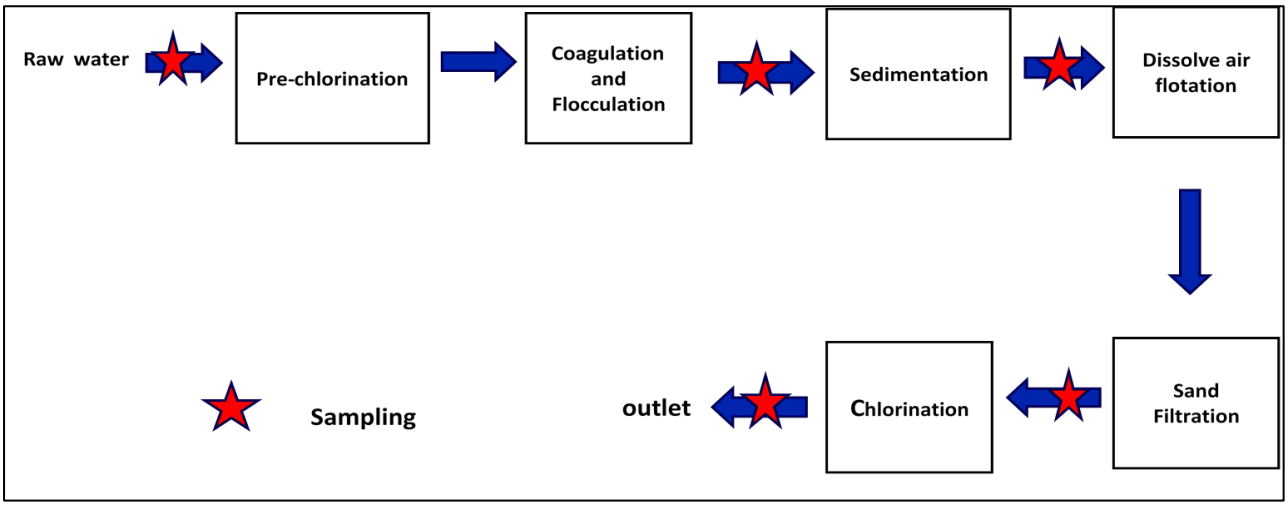
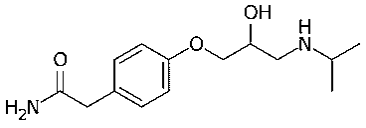
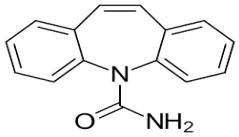
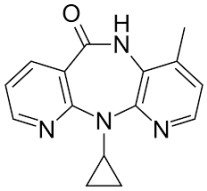
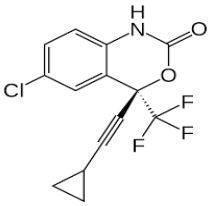
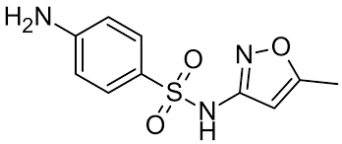


Figure 13: Depiction of Drinking Water Treatment Plant -3 Sampling Points

Table 5: Therapeutic class, structure and pKa value for emerging contaminants

EC name	Therapeutic class	Chemical structure	CAS No.	pKa	Reference
Atenolol	Beta blocker		29122-68-7	9.6	(Petrie et al., 2015, Patel et al., 2019)
Carbamazepine	Anti-convulsant		298-46-4	13.9	(Petrie et al., 2015, Rajendran and Sen, 2018)
Nevirapine	Antiretroviral		129618-40-2	2.8	(Petrie et al., 2015, Adeola and Forbes, 2022)
Efavirenz	Antiretroviral		154598-52-4	10.2	(Petrie et al., 2015, Adeola and Forbes, 2022)
Sulfamethoxazole	Antibiotic		723-46-6	1.6	(Petrie et al., 2015, Patel et al., 2019)

3.2.3 Experimental procedures

3.2.3.1 Working standard.

Individual pharmaceutical stock solutions were prepared by dissolving precise amounts of the powdered standard in various methanol concentrations based on their solubility. In 10 mL of MeOH, 10 mg of CBZ, ATN, NVP, EFV, and SMXZ were dissolved to produce a 1000 mg/L stock solution. The prepared stock solution was then filtered using 0.22µm nylon filters and stored at 4 °C in 12-mL dark amber vials. Individual stock solutions were dissolved in methanol to establish working standards in the following concentration ranges: (1.25, 3.25, 6.25, 12.5, 25, and 50) µg/L. Before uHPLC-MS analysis, all working standards were freshly prepared.

3.2.3.2 Solid phase extraction (SPE) sample preparation

The SPE procedure was developed and optimized using the Supelco HLB 200 mg/6 ml cartridge, since the selected SPE cartridge permits a wide range of pH selectivity (Lacey et al., 2008). An ultra-pure water matrix was used for the SPE optimized protocol to avoid matrix effect and unexpected interference. The determination of the ideal SPE conditions was conducted by introducing two sets of conditions. A 0.05 µg/L mixed standard (Efavirenz, Nevirapine, Atenolol, Sulfamethoxazole, and Carbamazepine) and 0.1 µg/L mixed standard spikes were considered the first and second batches, respectively. The mixed standard spikes were selected based on their concentration levels being above the limits of quantification (LOQ) and detection (LOD) for all ECs at the pre-concentration stage. Hypothetically, after the solid-phase extraction, the 0.05 g/L and 0.1 µg/L concentrations were expected to increase to 25 µg /L and 50 µg/L, respectively. Indicating pre-concentration of each EC 5 x 10^2-fold, leading to a reliable quantification signal in the uHPLC analysis. This also enabled the developed SPE method's efficacy to be measured.

3.2.3.3 Solid phase extraction optimization

The selected SPE HLB cartridge was connected to a 12-position SPE manifold, then preconditioned with 6 mL methanol and 6 mL of 0.1% acidified ultra-pure water at different pH ranges (3, 4.5, 5, 6.5, 7, and 8), at a flow rate of 2 mL min^{-1}. A 500-mL sample volume was loaded into the activated cartridge (Ferrer and Thurman, 2012, Mirzaei et al., 2017). After the sample was completely passed through the cartridge, it was vacuum dried for 5 minutes, washed with 6 mL of pH-modified ultrapure water, then dried again for 10 minutes. To elute the ECs from the loaded cartridges, 4 mL of [1:1] methanol/acetonitrile was used at a flow rate of 2 mL min^{-1} (Cai et al., 2015, Abafe et al., 2018, Guedes-Alonso et al., 2013). Extracted samples were dried at 30 °C under nitrogen gas before being reconstituted in 4 mL methanol for uHPLC-MS analysis. The ECs SPE percentage recoveries were calculated by comparing the concentration of ECs obtained after SPE extraction with the concentration before the extraction, equation (E.q.12) below.

$$SPE\%\ recovery = \frac{EC\ analytical\ responses}{EC\ spike} * \left(\frac{ECs\ elution\ volume}{Sample\ volume}\right)\ x\ 100 \qquad (12)$$

The first EC trail led to a recovery percentage of less than 50% which was not acceptable. In the subsequent trails, following steps were modified from the first trial conditions: a) At the wash stage, the wash volume was lowered from 6 mL to 4 mL; b) at the elution step, ECs were eluted using a 4 mL [ACN/MeOH] solvent divided into two 2 mL aliquots. To enhance elution efficacy, a 2-minute interval was made between the introductions of the two 2-mL solvents into the cartridge; c) the sample loading flow rate was reduced from 2 mL min^{-1} to 1 mL min^{-1} and d) the reconstitution volume was reduced from 4 mL of methanol to 1 mL. The changes made to the first trial SPE procedure were credited to the second trial SPE procedure. The SPE-optimized method was evaluated and validated by using environmental samples collected from selected KZN drinking water treatment plants.

3.3. Detection of emerging contaminants in drinking water treatment plants using the optimized method

3.3.1 Sample preparation

The 2-liter sample collected at each DWTP treatment unit was divided into four 500-mL sample portions. Each 500-mL aliquot sample was spiked with a mixed standard (SMXZ, ATN, EFV, NVP, and CBZ) in ascending concentrations of (10, 20, 30, and 40) µg/L to conduct a standard addition analysis (Cimetiere et al., 2013). The spiked samples were subjected to the optimized SPE conditions. The 4 mL extracts collected from the SPE experiment were dried with nitrogen inert gas at 30 °C to remove water content and prevent further oxidation of the investigated ECs. The samples were then analysed by uHPLC-MS.

3.3.2 Analytical methods

3.3.2.1 Ultra-High Performance Liquid Chromatography-mass spectroscopy (uHPLC-MS) optimization

A 10 µg/L standard for each of the five selected ECs was prepared in LC-MS grade methanol. The prepared standard was injected into the mass spectrometer, and a mass scan from 50 to 1000 Dalton (Da) was performed to identify the parent ion and daughter ion for each of the EC. Table 19 Appendix 2 lists the optimal curtain gas (CUR), collision gas (CAD), ion spray (IS) voltage, temperature (TEM), nebulizing gas 1 (GS1), and nebulizing gas 2 (GS2) MS ion source parameters. Another freshly prepared 10 µg/L standard for each of the investigated ECs was injected from the uHPLC compartment without a column into the MS ion source to find the optimal MS settings for each EC.

3.3.2.2 Chromatographic Separations

Determination of occurrence levels of selected ECs in drinking water samples analysis and solid phase extraction optimization were conducted using uHPLC-MS. The analysis was performed using SCIEX uHPLC 5500 equipped with a mass spectrometer MS, with a triple-quadrupole mass analyzer *(m/z* range: 0-3000; ionization modes: ESI+/-). The uHPLC column temperature was set at 30℃ and the injection volume was 5 µL. The analysis was performed using a non-polar Shim-pack GISS C18 column from Shimadzu, with particle size of 1.9µm, internal diameter of 2.1 mm and length of 100 mm. The optimized gradient consists of 0.1 % (v/v) formic acid in methanol and 0.1 % (v/v) formic acid in LC/MS water.

3.3.2.3 Method validation and Statistical method analysis

The proposed methods were validated according to the european guidelines (Pihlström et al., 2017, Rizzo et al., 2020).The instrumental and experimental parameters that were examined encompassed selectivity, linearity, detection (LOD), quantification limits (LOQ), coefficient of variation (CV), matrix effect (ME%), and recovery. Hence, uHPLC gradient elution parameters, including calibration curves for each EC's parent and daughter ions, and chromatograms of all five investigated ECs, are displayed in Table 20 Appendix 2, including Figures 29 and 30 Appendix 3, respectively.

Table 6 displays the uHPLC optimized parameters for the selected emerging contaminants, which include LOD, LOQ, and CV.

Table 6: The uHPLC optimized parameters for the selected Emerging contaminants

ECs name	pKa	Q1 Mass (Da)	Q3 Mass (Da)	Dwell time (msec)	DP (volts)	CE (volts)	CXP (volts)	LODs (µg/L)	LOQs (µg/L)	CV
Atenolol	9.6	267.003	185.010	150	30	40	10	1.28	3.87	0.711
Carbamazepine	13.9	237.1	193.50	150	30	20	10	0.59	1.79	0.713
Efavirenz	10.2	316.0	244.0	150	100	20	8	0.46	1.39	0.711
Sulfamethoxazole	1.6	254.108	155.900	150	30	20	8	0.56	1.72	0.72
Nevirapine	2.8	267.128	226.500	150	100	40	10	0.38	1.15	0.711

3.3.2.4 Matrix effect

The equations (E.q.13) below, was used to figure out the matrix effect (%ME) in the drinking water treatment plant DWTP effluent samples that were selected. Matrix effect estimation required comparing the slopes of standard curves dissolved in the extraction solvent with the slopes of calibration curves tailored to the specific matrix. To determine the matrix-matched slope, the calibration curve of effluent samples spiked with a known concentration range (10, 20, 30, 40) µg/L was extrapolated and compared with the slope obtained from the calibration graph, which was constructed using a known concentration range (10, 20, 30, and 40) µg/L of each EC analytical standard in methanol, it was multiplied by 100 (Walorczyk, 2014, Schreiber and von Czapiewski, 2010).

$$\mathrm{ME\%} = \frac{1 \quad - Slope_{solvent}}{Slope_{matrix}}\ x\ 100 \qquad (13)$$

3.3.7 Statistical method

All mean comparisons (t-tests), and ANOVAs on the EC data were performed using Origin software. One-way ANOVAs was used to determine significant differences between different EC removals and the significance of all analyses being determined with an alpha level of 0.05.

3.4 Human health risk assessment

Risk quotients (RQs) are used to represent health risks to humans. RQs are defined as the ratio between the exposure concentration and the threshold for an adverse effect in drinking water. Using the following equations (E.q.14 and E.q. 15) (Labad et al., 2023), the RQs for each selected EC were determined.

$$RQ = \frac{Cmax}{DWEL} \tag{14}$$

$$RQ = \frac{Cmean}{DWEL} \tag{15}$$

The maximum EC concentration (C_{max}), the average EC concentration (C_{mean}), and the drinking water equivalent level (DWEL) are all written in ng/L. Provided that the RQ values are smaller than 1, the exposure to the selected EC has fewer negative effects on the DWEL threshold (Labad et al., 2023). However, the DWEL values for each EC had to be determined before the RQ values could be determined. Thus, the following equation (E.q.16) was used to calculate the DWEL for each EC:

$$DWEL\ (\frac{ng}{L}) = \frac{ADI \text{ x } BW}{DWI \text{ x AB x FOE}} \tag{16}$$

Using acceptable daily intake (ADI), body weight (BW), daily water consumption rate (DWI), (AB) being the portion of the substance that enters the digestive system, regarded as being equivalent to 1 in terms of absorption, and frequency of exposure (FOE) acquired from literature for each EC. The DWEL values determined for the following categories—toddler (10–36) months, adults (18–50) years, and elderly people (50–75) years— body weights of (20, 65, and 60) kg — DWI (0.75, 2.3 and 1.8) litre respectively, were assumed to be reasonable. A tabulated depiction is shown in Table 7. Using the calculated DWEL values, the EC's RQ_{max} and RQ_{mean} values were also calculated for each age group, which are the maximum and mean risk quotients, respectively.

Table 7: Parameters for Human Health Risk Assessment of Selected ECs - Body Mass Index, Age Group, and Water Litre Consumption

	(Toddler)		(Adults)		(Elderly people)		
ECS	**BW (kg)**	**DWI (Litre)**	**BW (kg)**	**DWI (Litre)**	**BW (kg)**	**DWI (Litre)**	**ADI (ug/kg) per.day**
Atenolol	20	0.75	65	2.3	60	1.8	0.4
Carbamazepine	20	0.75	65	2.3	60	1.8	2.9
Sulfamethoxazole	20	0.75	65	2.3	60	1.8	3.8
Efavirenz	20	0.75	65	2.3	60	1.8	0.6
Nevirapine	20	0.75	65	2.3	60	1.8	0.2

ADI's reference: https://www.healthline.com, Sengar and Vijayanandan, (2021), Prosser *et al.* (2014)

3.5 Results and Discussion

3.5.1 Solid phase extraction optimization

The SPE experiments conducted using the Shim-pack GISS C18 column for the detection and quantification of the selected ECs were maintained within a pH range of 3 to 8. This pH range was chosen to preserve the column and ensure its optimal performance. The pH limit threshold of the Shim-pack GISS C18 column is between 1 and 10, which encompasses the selected pH range of the experiments. By operating within this range, factors such as sensitivity, reliability, quantification, and precision of the experiments are optimized, as these properties are influenced by the pH conditions (Shimadzu, 2019). Consequently, experiments conducted below pH 3 and above pH 9 were excluded to prevent potential damage to the column and to maintain consistent and accurate results. Additionally, the pKa values of the selected ECs were taken into consideration when determining the pH range for the experiments. These decisions were made to ensure the reliability and accuracy of the analysis performed using the Shim-pack GISS C18 column. The results of the first trial throughout the selected pH 3– pH 8 range showed higher recoveries at pH 3 for most of the investigated ECs, displayed in Table 8 below. In the first trial experiment, as the pH increased gradually from 3 to 8, there was a gradual decline in the recoveries of all selected ECs, but a significant decline was notably seen in Atenolol and Sulfamethoxazole during solid-phase extraction. The SPE recoveries of atenolol and Sulfamethoxazole were not detectable between pH 6, 7 and 8. An overall average < 50% recovery after SPE was reported, which was considered inadequate because an acceptable SPE method should provide recovery rates ranging between (70-120) percentages (Powley *et al.* 2005). In the second trial, when the pH was set to 8, only two out of the five ECs (Nevirapine and Carbamazepine) exhibited SPE recoveries > 99%. However, when the pH was adjusted to 3, four out of the five ECs (Efavirenz, Nevirapine, Carbamazepine, and Sulfamethoxazole) demonstrated SPE recoveries ranging between 57% and 80%. Atenolol, on the other hand, exhibited a 30% SPE recovery at pH 3, which, while poor, was higher compared to the previous trial and the other pH values (6.5 and 8). Consequently, to select a more reliable SPE method within the examined pH range, the SPE conditions at pH 3 were considered ideal for achieving optimal extraction of the five selected ECs. Across all the selected ECs, an average SPE recovery of 64% was observed at pH 3.

The specific SPE recoveries for each EC at pH 3 were as follows: 71% for Carbamazepine, 80% for Nevirapine, 80% for Efavirenz, 57% for Sulfamethoxazole, and 30% for Atenolol. According to a study conducted by de Oliveira *et al*. (2019), the SPE recovery of Atenolol was found to be < 20% using Strata^{TM-X} (200mg cartridge) and acetonitrile/methanol (ACN/MeOH) eluent. Similarly, in a study conducted by Ngwenya and Mahlambi (2023), the SPE recovery of Efavirenz was reported to be < 50% using Oasis HLB cartridge SPE sorbents (60 mg, 3 mL) and ACN/MeOH eluent. In comparison, in this study, Efavirenz displayed SPE recovery 30% higher than what was reported using Oasis HLB cartridges.

Table 8: Optimized Conditions for Solid Phase Extraction of Selected Emerging Contaminants

ECs	First trial % Recovery							Second trial % Recovery		
	pH 3	**pH 4**	**pH 4.5**	**pH 5**	**pH 6**	**pH 7**	**pH 8**	**pH 3**	**pH 6.5**	**pH 8**
Atenolol	2	-	-	-	-	-	-	30	15	18
Sulfamethoxazole	47	16	14	12	-	-	-	57	30	41
Carbamazepine	31	31	30	14	<50	<50	<50	71	85	118
Nevirapine	38	36	36	23.2	<50	<50	<50	80	41	119
Efavirenz	36	36	36	24	<50	<50	<50	80	30	19

Therefore, the utilization of Supelco HLB cartridges in this study, in comparison with the application of Strata^{TM}-X and Oasis HLB cartridges, demonstrates a consistently low yield of solid-phase extraction for Atenolol and Sulfamethoxazole. It should be noted that the presence of interfering substances in the sample matrix can have a detrimental effect on the extraction efficiency of atenolol and Sulfamethoxazole. Additionally, factors such as hydrophobicity, molecular size, and polarity can influence their interaction with the SPE sorbent material, thereby resulting in decreased recovery (Safari et al., 2019). The pKa values of all ECs also influenced their SPE recoveries (society, 2017).

In this study, conducted at pH 3, it was observed that ECs with pKa values in the acidic medium exhibited higher recoveries compared to ECs with pKa values in the basic medium. This finding is consistent with the results reported in the study by (Raabová et al., 2021), which investigated the role of pKa in analytes. However, except for Nevirapine and Carbamazepine, these ECs demonstrated good recoveries in both mediums because they have similar pKa values in both mediums. Carbamazepine has a pKa of 3.8 in acidic medium and 13.9 in basic medium, while Nevirapine has a pKa of 2.8 in acidic medium and 11 in basic medium (Silberberg 2012). Both Sulfamethoxazole and Atenolol had low SPE recoveries that were attributed to ion suppression generated by the combination of all investigated ECs in the ultrapure matrix, which interfered with their instrumental signal-to-noise ratio (Sanchís *et al.* 2012). Since the ECs' pKa values were not in the same pH medium, the SPE recoveries for all five ECs didn't yield in a uniform manner. Nevirapine, Carbamazepine, and Efavirenz showed steady improvement in SPE recovery, while Atenolol and Sulfamethoxazole displayed lower recoveries.

3.5.2 Matrix effect

Matrix interference and competing pollutants present in the DTWP effluent sample may influence how the target ECs respond in the chromatographic analysis. In mass spectrometry, particularly when analyzing complex samples, the phenomena of ion suppression and ion enhancement can be observed, and they provide significant insights into the reliability and precision of the results of analysis (Antignac *et al.,* 2005). If the matrix effect percentage (%ME) of the investigated ECs is above 100 percent, then those ECs exhibit ion enhancement (Van Eeckhaut *et al.,* 2009). Whereas a value below 100 percent indicates ion suppression (Zhou *et al.,* 2017). The average matrix effect percentage values for each EC found in the post-chlorination treatment units are shown in Table 9. Low matrix effect percentages were observed for atenolol and sulfamethoxazole, with values of 39% and 50%, respectively. These percentages were notably different from a study by Rossmann *et al*. (2015), which reported a matrix effect percentage of less than 20% for atenolol. In this study, atenolol exhibited a 19% higher matrix effect percentage compared to their findings. However, when compared to a study by Cardoso *et al.* (2011) in surface and public supply water, matrix effect percentages for atenolol and sulfamethoxazole were approximately 20% lower on average. On the other hand, high matrix effect percentage values were observed for Nevirapine, Efavirenz, and Carbamazepine, with values of 84%, 80%, and 74%, respectively.

These values were similar to the matrix effect percentages reported by Mokgope *et al.* (2022) in the investigation of ARVs in wastewater for Nevirapine and Efavirenz. However, the matrix effect percentage for carbamazepine reported in this study was considerably lower (less than 7%) compared to the 81% reported by Sodré and Cavalcanti (2018) for carbamazepine in water sources within the Brazilian Federal District. This study revealed variations in matrix effect percentages for different ECs, with atenolol, carbamazepine, and sulfamethoxazole showing lower percentages compared to previous studies, while Nevirapine and Efavirenz exhibited higher or similar percentages as reported in relevant research. Among the selected ECs, atenolol and sulfamethoxazole exhibited significant ion suppression, while the other three ECs showed minimal ion suppression.

Table 9: Matrix Effect Percentage of Selected Emerging Contaminants

Emerging contaminants	Avg. % matrix effect
Atenolol	39
Carbamazepine	74
Nevirapine	84
Sulfamethoxazole	50
Efavirenz	80

3.5.3 Emerging Contaminants removal efficacies in various treatment units

3.5.3.1 Emerging Contaminants removal during Coagulation

Coagulation is the first step in the removal of ECs in a drinking water treatment plant. The process of coagulation involves two main mechanisms: charge neutralization and polymer bridges (Alazaiza *et al.* 2022). Figure 14 below illustrates the coagulation process employed during drinking water treatment.

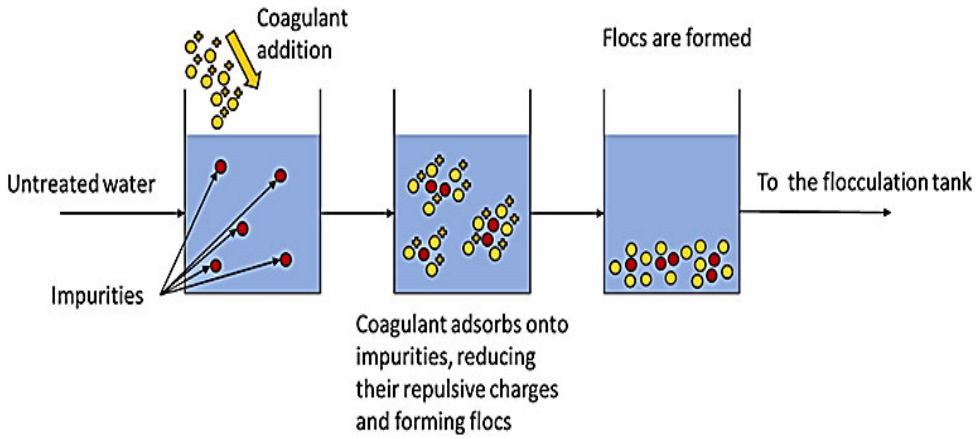


Figure 14: Coagulation process employed during drinking water treatment(Turner and Oliver, 2019)

The charge neutralization process is responsible for destabilizing and removing suspended particles and ECs from raw water by neutralizing their electrical charges (Ødegaard 1988). Complementary to charge neutralization, the polymer bridging process acts as a bridge between particles and ECs to promote their coagulation. Basically, the polymers act similarly to charge neutralization by destabilizing the charges, leading to flocculation and EC removal. The polymer chains are then formed through the compression of the double layer, electrostatic adsorption, and bridge formation (Jiang 2015). This leads to the facilitation of the ECs treatment by removing colloids (Kooijman *et al.* 2020; Macherzyńskia *et al.* 2021). In reference to pharmaceutical EC removal, coagulation in treatment plants is known to remove approximately less than 25% (Bienkowski 2013). The percentages of the selected ECs removed in the coagulation treatment unit are represented in box and whisker plots, which are shown in Figure 15 below. The on-site tests, namely: TDS%, DO%, salinity, conductivity (µS/cm), and temperature, were conducted in the coagulation unit. The results of these tests are displayed in Table 18 Appendix 2. Observations showed that Nevirapine and Efavirenz, both in the 75th percentile, had the highest removal percentages of 79% and 58%, respectively. Carbamazepine and sulfamethoxazole, also in the same percentile, had a similar removal rate of 38%, while atenolol had the lowest removal rate of 18%. The median (50 percentile) of all selected ECs resulted in an average removal rate of 19.87% for all five ECs. These results indicated that Efavirenz and Nevirapine, which are antiretroviral drugs, exhibited a higher susceptibility to coagulation treatment compared to the other three selected ECs belonging to different category classes.

Both antiretroviral drugs may have a higher affinity for the coagulants employed in treatment, resulting in greater interactions and increased vulnerability to the coagulation process (Lapointe et al., 2020). As illustrated in Figure 15, the median of all selected ECs resulted in an average removal rate of 20% for all five ECs.

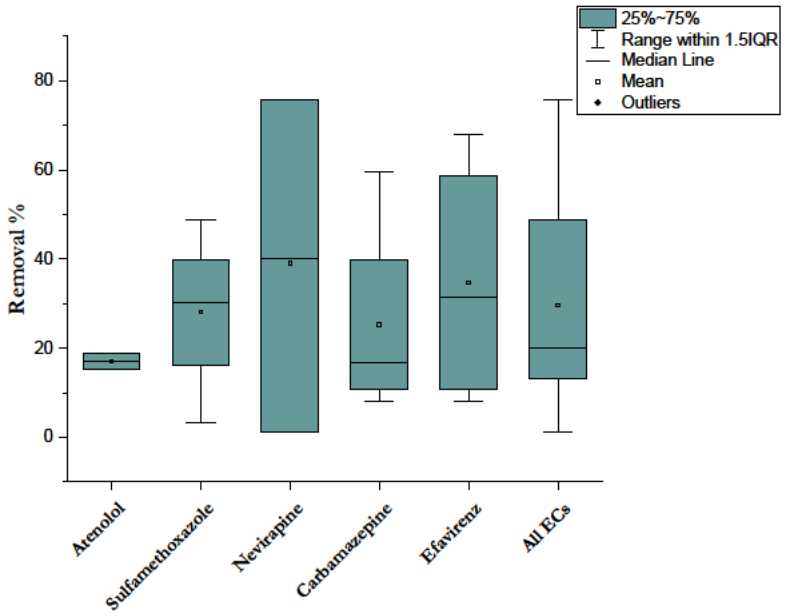


Figure 15: Percentage Removal of Emerging Contaminants in Coagulation Treatment Unit

3.5.3.2 Emerging Contaminants removal during Sedimentation

The sedimentation process of drinking water treatment typically occurs after coagulation and flocculation, but before filtration in a conventional water treatment process (O'Melia 1998). Regarding the treatment of pharmaceutical EC present in water, sedimentation keeps solid particles suspended in the liquid medium while imparting viscosity to the liquid medium (Kumar *et al.* 2009). Then separate them from the suspending fluid (Adomat and Grischek 2021) by using gravity to pull down heavier suspended solids, including ECs and debris, to the bottom containment unit (Fitch 1979).

Depending on the nature of the solids, the treatment process is known to remove approximately 60%–80% of the suspended solids, pharmaceuticals, and turbidity (Chapman *et al.* 2014). Figure 16 below, shows how much of the selected ECs are removed by the sedimentation step. The on-site test in the sedimentation unit is shown in Table 18 Appendix 2. Using gravity, the sedimentation unit caused heavier debris particles, such as silt, clay, sand, bacteria, algae, oil, grease, and EC metabolites, to sink to the bottom of the tank, forming a layer of sludge. Meanwhile, lighter particles, such as oil and grease, would float to the surface and be removed by skimming. The supernatant formed between the floating and sludge layers was then transferred to the next treatment unit. According to the findings, it was observed that Carbamazepine, in the 75th percentile, had the highest removal percentage of 75.51%. In the same percentile, Sulfamethoxazole and Nevirapine had removal rates of 49.7% and 45.67%, respectively, while Efavirenz and Atenolol exhibited the lowest removal rates of 33.61% and 29.61%, respectively, with outliers observed at 57.69% and 63.06%, respectively. The removal rate of Atenolol increased from 18% in the coagulation unit to an average of 29.61%, was due to the combination and effectiveness of the selected coagulant from the coagulation treatment unit and the gravitational force in the sedimentation treatment unit. The median of all selected ECs resulted in an average removal rate of 32.73% for all five ECs.

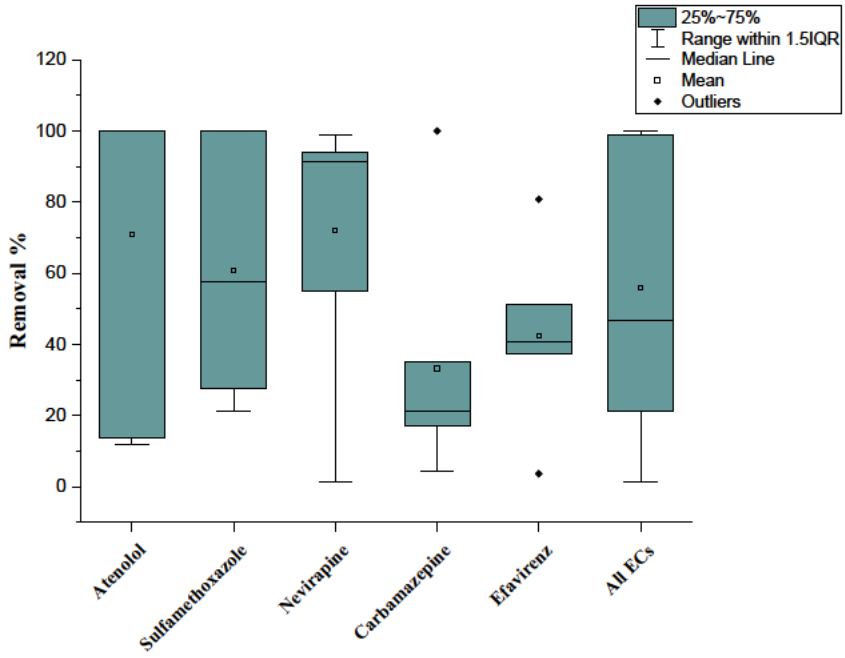


Figure 16: Percentage Removal of Emerging Contaminants in Sedimentation treatment unit

3.5.4.3 Emerging Contaminants removal during Sand filtration

Sand filtration is known to removes solid particles, and pharmaceutical waste through two mechanisms, namely, sedimentation and adsorption (Verma *et al*.2017; Li, Zhou and Campos 2018). The sand particles in the filter bed create a medium where solid particles, including pharmaceuticals, settle out from the water and become trapped in the sand filter. Which is particularly effective for larger particles and solids that are present in the water (Hamoda et al., 2004). Sand filtration can also remove pharmaceuticals through adsorption. The surface area of the sand media is required to be large, with many tiny crevices and pores. When emerging contaminants-containing water passes through the filter bed, the pharmaceutical, ECs molecules adsorb onto the surface of the sand particles, effectively removing them from the water (Dalahmeh et al., 2018). Sand filtration has been observed to remove micro pollutants with a removal efficiency of approximately 70%, whereas granular activated carbon (GAC) filtration removes micro pollutants with an 81% removal efficiency. Consequently, sand filtering as a conventional treatment process can still be regarded as robust when matched with modern treatment processes (Velasco *et al*. 2023). Figure 17 below shows the percentage of ECs in the sand filtration treatment unit. The on-site test in the sand filtration is shown in Table 18 Appendix 2. In the sand filtration treatment unit, the sand bed effectively removed suspended solids, including ECs, from the water. As the water flowed through the sand filter, the sand bed effectively captured the ECs and other impurities, resulting in a cleaner effluent. Based on the results, it was observed that sulfamethoxazole, in the 75th percentile, had the highest removal percentage of 72.85%. In the same percentile, Efavirenz and Atenolol had removal rates of 65.53% and 48.73%, respectively. Certain ECs, such as carbamazepine, were merely affected or removed during the sand filtration procedure. According to literature, it was assumed that sand filtration treatment units ranged from 0 to 25% (Li *et al*., 2022). Both carbamazepine and nevirapine displayed similar trends in removal rates of 36.22% and 32.72%, respectively. Which had the lowest reported removal rate in comparison to the other three investigated ECs. The lower removal rate of the two ECs may be attributed to their hydrophilic nature, which may have affected their removal efficiency. Since they probably have low log KOW values, indicating high hydrophilicity, and needed the ECs to properly crystalize to become suspended solids (Rizzo *et al*. 2015). Which would increase the sand filter bed's efficiency in capturing and significantly removing these two ECs. The median of all selected ECs resulted in an average removal rate of 31.91% for all five ECs.

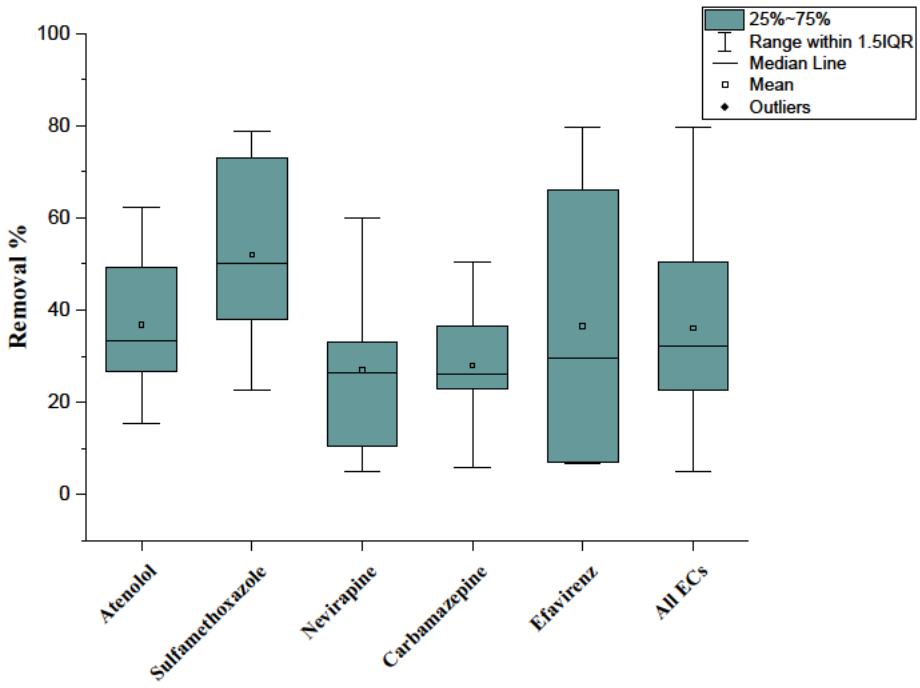


Figure 17: Percentage Removal of Emerging Contaminants in sand filtration treatment unit

3.5.3.4 EC removal during Chlorination

In the chlorination treatment unit, hypo-chlorinators, which are motor-driven pumps are used to add chlorine to the water, draw hypochlorite solution from a holding chamber and inject it into the water to be treated, (Lindmark *et al.* 2022). The amount of chlorine added during chlorination varies by application, with typical ranges between 0.1 and 0.5 ppm prior to water filtration to prevent germination on the filter (Zheng *et al.* 2017). Chlorine is added in two stages of the water treatment plant, pre-chlorination, and post chlorination. Pre-chlorination involves adding chlorine to the raw water after screening and before flash mixing, which is an initial step in the treatment process (Jamaly *et al.,* 2014). This helps to disinfect the water from pharmaceutical waste and control the growth of microorganisms (Berry *et al.* 2006). On the other hand, post-chlorination involves adding chlorine after the water has gone through the main treatment processes, such as filtration or sedimentation, and just before it is stored in the clear water reservoir (Gray, 2014). This allows for a sufficient contact time for the chlorine to act and further disinfect the water before it is distributed for consumption (Lindmark *et al.*, 2022).

Figure 18 below shows the removal percentage of ECs during the chlorination step. The residual chlorine concentration reported in the chlorination unit was 0.5 mg/L and the pH was 7.6. During the treatment processes, which encompass coagulation, sedimentation, and sand filtration, it was observed that among the five investigated ECs, namely sulfamethoxazole, atenolol, and Nevirapine, there was a noticeable increase in the degree of degradation in comparison to Efavirenz and carbamazepine. This difference in degradation was primarily attributed to 0.5 mg/L chlorine in the treatment unit. This chlorine content contributed to the enhanced removal of these three ECs. Chlorine, with its oxidative and disinfection properties, facilitated the breakdown of the susceptible ECs, ultimately leading to improved treatment efficiency within the chlorination treatment unit. Based on these findings, Atenolol, Sulfamethoxazole, and Nevirapine, in the 75th percentile, had the highest removal percentages of 100%, 100%, and 93.35%, respectively. In the same percentile, Efavirenz and Carbamazepine had removal rates of 51.31% and 34.39%, respectively. In several drinking-water plants in Boston, America, it was reported that the chlorination treatment units reduced the concentrations of some prescription drugs, such as carbamazepine, by 75% (*Drugs in the water* 2011). In contrast, Carbamazepine had removal rate of 51.31%, which was less by 23.69 % than that which was reported in Boston. Outliers were also observed in Efavirenz at 3.1% and 80%, and Carbamazepine at 100%. The outliers were probably due to the presence of other chemicals or compounds that interfere with the ECs removal process. The median of all selected ECs resulted in an average removal rate of 46.14% for all five compounds. Out of the five selected ECs, Sulfamethoxazole demonstrated the highest removal rate among the four treatment units that were chosen. In addition, the chlorination treatment unit showed the highest median ECs removal rate, which amounted to 46.14%. This study demonstrated the effectiveness of chlorination in removing ECs from drinking water, with atenolol, sulfamethoxazole, and nevirapine having the highest removal percentages. The study further provided a comparative analysis of chlorination results, highlighting the importance of considering operational conditions when designing water treatment processes. Hence, understanding the removal efficiency of ECs can help optimize treatment plants and, importantly, drinking water quality. Since chlorination is crucial for public health protection and environmental impact mitigation, in drinking water.

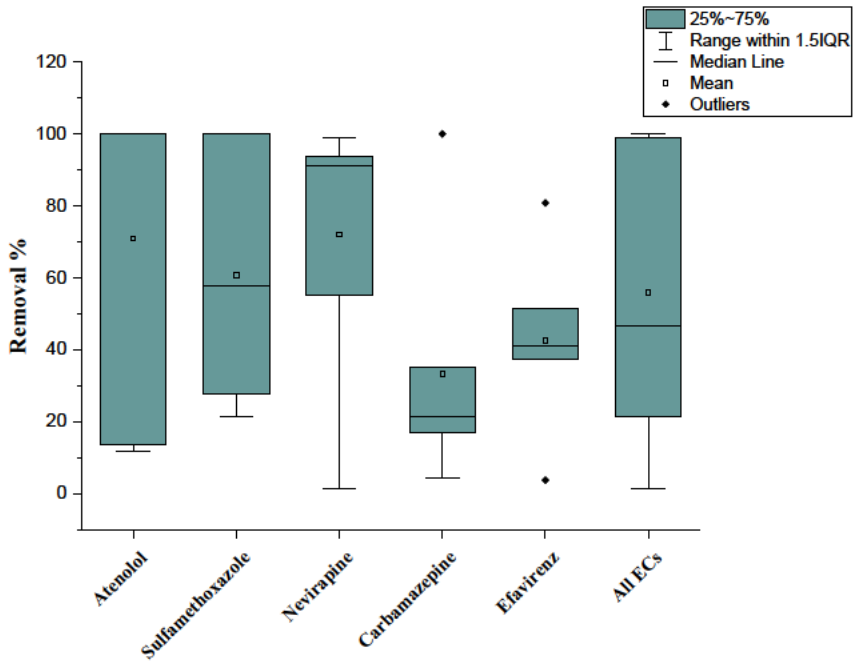


Figure 18: Percentage Removal of Emerging Contaminants in chlorination treatment unit

3.5.4 Emerging contaminants occurrence levels and their removal in selected drinking water treatment plants

Selected ECs were detected in all the samples analysed in this study, however in low concentration. The concentrations observed were below the LODs and LOQs as reported in Table 10. Even though the EC concentrations were below the detection limit (BDL), the ECs had 100% detection frequency (DF) in the selected treatment (raw water, coagulation, sedimentation, sand filtration and chlorination) units of the selected DWTPs. The detection frequency (%) measures the frequency with which a certain EC is identified in a sample. It is determined by dividing the number of samples containing ECs by the total number of samples analysed (Al-Odaini *et al.* 2012).

Table 10: Occurrence level of ECs in the influent and effluents of DWTPs

ECs	Category	Surface water (Raw water) (ng/L) (N=5)				Effluent DWTP (ng/L) (N=5)			
		Min	Max	Mean	Detection frequency (%)	Min	Max	Mean	coefficient of variation
Atenolol	**Beta blocker**	64.42	330.52	197.47	BDL	13.33	77.54	45.44	0.89
Carbamazepine	**Antiepileptic**	43.52	193.85	118.69	BDL	19.40	28.19	23.80	0.94
Efavirenz	**Antiretroviral**	41.11	271.13	156.12	BDL	5.23	38.36	21.80	1.07
Nevirapine	**Antiretroviral**	24.35	303.77	164.06	BDL	0.14	48.02	24.08	1.05
Sulfamethoxazole	**Antibiotic**	22.57	206.17	114.37	BDL	2.34	26.99	14.67	1.09

The average removal efficiencies of each EC between raw water effluent and DWTP effluent were Sulfamethoxazole (87.17%), Nevirapine (85.32%), Carbamazepine (79.94%), atenolol (76.99%), and Efavirenz (70.89%). Referring to Table 10, the following ECs, Atenolol, Nevirapine, and Efavirenz, may not exhibit the true concentration values and removal efficiencies, due to ion suppression caused by the matrix effect existing in the DWTP influent and effluent drinking water samples. Using one way-ANOVA analysis, in this study, a paired sample t-test was employed to examine the mean concentration of ECs in the surface water effluent and the mean concentration of ECs in the DWTP effluent. The statistical analysis revealed a t-statistic of 10.92, indicating a substantial difference between the means of the two data sets. Including, the obtained p-value (3.98×10^{-4}), which was found to be lower than the predetermined significance level of 0.05. An important point to consider is that the selected ECs were found only in trace amounts (≤ng/L), indicating that the toxic disinfection by-products, formed during the degradation and removal of these ECs through chlorine disinfection processes, maybe present at significantly lower levels. This finding serves as a positive indication for the safety and regulation of drinking water quality. However, it is also important to continue monitoring the presence of these ECs in drinking water treatment plants, as their concentrations may increase due to changes in influent source because of increased human activity. It is crucial to ensure that drinking water treatment processes can effectively remove and reduce the concentrations of these ECs to acceptable levels according to drinking water guidelines.

3.5.5 Human health risk assessment

The risk quotient is a commonly used method for assessing the potential risk of exposure to ECs (Kondor et al., 2021). The RQ_{max} values for toddler, adults, and elderly people, in increasing order, are as follows: atenolol (0.03-0.015), carbamazepine and sulfamethoxazole (0.005-0.001), efavirenz (0.02-0.005), and nevirapine (0.058-0.028). All the RQ_{max} and RQ_{mean} values that were obtained were lower than 1, which indicated that the EC occurrence levels were not high enough to pose a threat to human health. The highest RO_{max} and RQ_{mean} values were seen under Nevirapine in toddler category, which suggested that the Nevirapine occurrence level in the KZN drinking water supply needs to be continuously monitored and further reduced for the benefit of toddler's health. The elimination half-life of nevirapine in adults is approximately 45 to 225 hours, or about 9.4 days. This refers to the time it takes for half of the drug concentration to be eliminated from the body of a fully grown individual (Drugs.com, 2022, Medicine.com, 2020). It's important to note that the elimination half-life may differ in toddlers due to their smaller body mass and potentially different immune strength. In toddlers, it may take two to three times as long for the drug to be eliminated compared to adults. The relationships between the EC's RQ_{max} and RQ_{mean} values for various ages are shown in Tables 11, and Figure (19-20), respectively.

Table 11: Maximum and Mean Average Risk Quotients of Selected Emerging Contaminants

	RQmax			RQmean		
EC name	**Toddler**	**Adults**	**Elderly people**	**Toddler**	**Adults**	**Elderly people**
Atenolol	0.0310	0.0292	0.0248	0.0185	0.0175	0.0148
Carbamazepine	0.0025	0.0024	0.0020	0.0015	0.0014	0.0012
Sulfamethaxazole	0.0020	0.0019	0.0016	0.0011	0.0011	0.0009
Efavirenz	0.0169	0.0160	0.0136	0.0098	0.0092	0.0078
Nevirapine	0.0570	0.0537	0.0456	0.0308	0.0290	0.0246

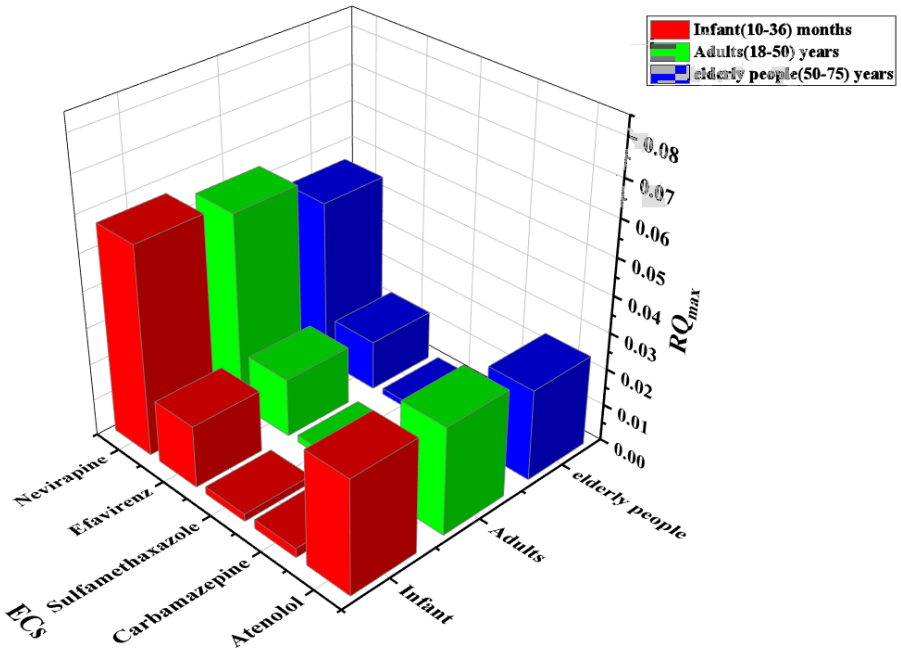


Figure 19: Assessment of Maximum Risk Quotients for Selected Emerging Contaminants

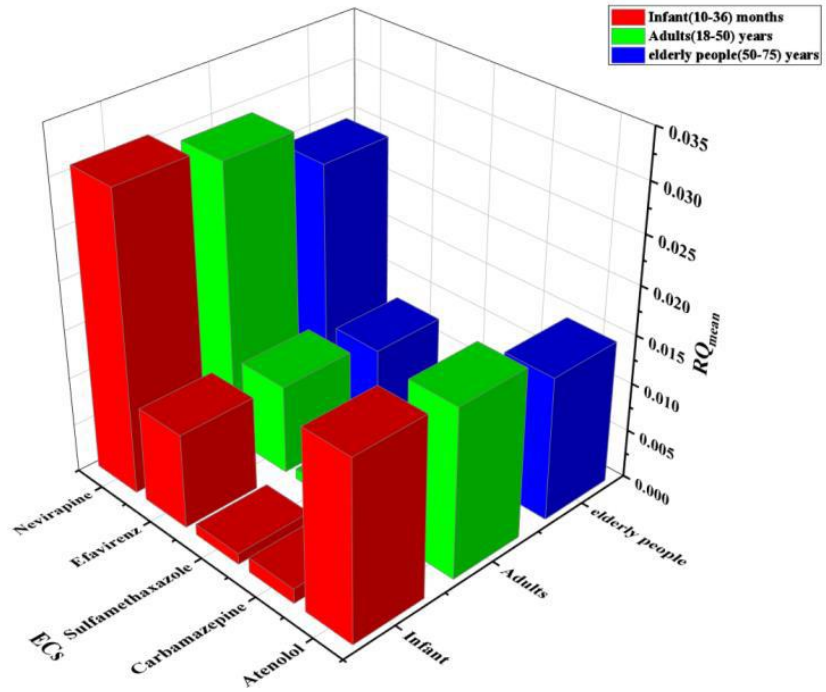


Figure 20: Assessment of Mean Risk Quotients for Selected Emerging Contaminants

3.5.6 Hazard Analysis by Critical Control Points system

The EC occurrence levels, selected disinfectant and operational parameters that may cause hazards to be introduced into or not removed from the drinking water were prioritized in the HACCP analysis. From the surface water effluent to the post-chlorination treatment unit, risk assessment is the key to recognizing hazards, rating their severity, and finding the controls in the system that manage those risks in an orderly way (Pierson, 2012, Tsitsifli and Tsoukalas, 2021). A flow diagram of the DWTP 1, DWTP 2 and DWTP 3 can be observed in Figure (9-11) depiction. Each potential risk to water quality was identified, and procedures were put in place to mitigate those risks. The selected drinking water treatment plants were subjected to a semi-qualitative risk assessment. It should be highlighted that the water treatment facility is not responsible for the water quality of the surface water effluent. The CCPs are defined by a series of technique decisions (Havelaar 1994; Mullenger *et al*.2002), the graphical strategy is shown in Figure 21 below.

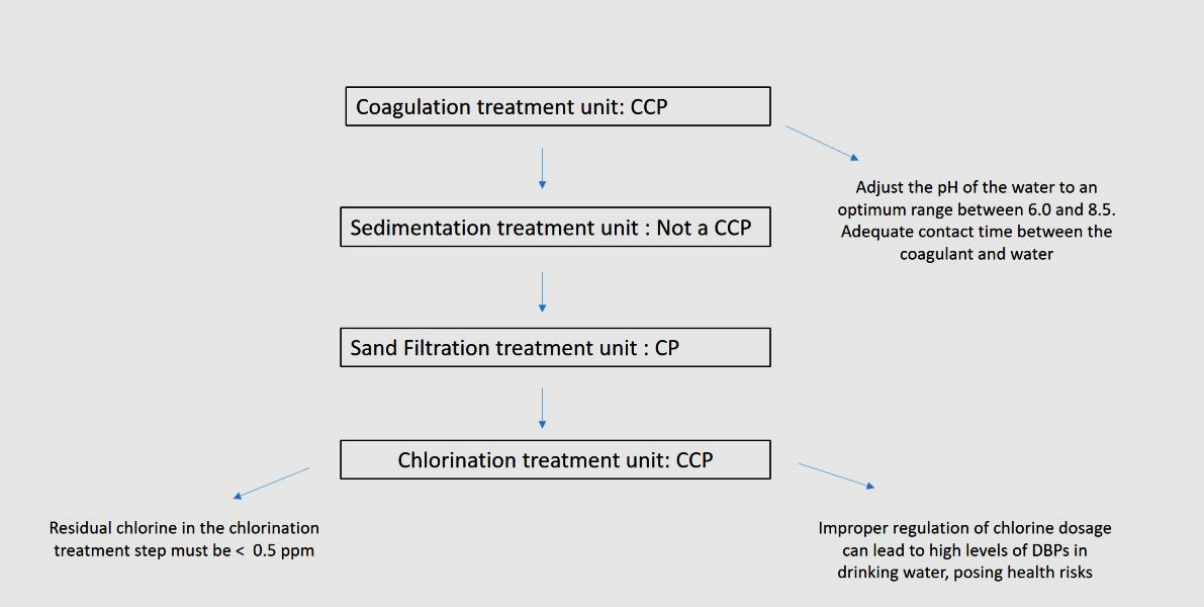


Figure 21: CCP Skeleton Diagram: Illustration of Critical Control Points in the Process

The HACCP plan comprises the treatment process stages, recognized risks, preventive measures, calculated critical control points, a monitoring system, critical limits of CCP monitoring parameters, and required corrective actions, and the CCPs are considered in this condition (Tavasolifar et al., 2012). Managing the residual chlorine dosage in the chlorination process is critical for reducing the formation of trihalomethane by-products, while preserving disinfection efficacy. In this study, the coagulation unit displayed the lowest average EC removal rate, above the rest of the treatment units. For this observation, coagulation was considered a CCP. Hence, to increase the efficacy of coagulation treatment in water treatment processes, it is important to adjust the pH of the water to an optimum range between 6.0 and 8.5 (Rosińska and Dąbrowska, 2021). Lime and sodium hydroxide are commonly utilized in water treatment to change pH. Lime, which contains calcium ions, provides both pH adjustment and coagulation whereas NaOH is added to raise pH to an ideal range of 6.0-8.5 for effective coagulation (Jiang, 2015). Also, to optimize the coagulant dosage, an appropriate coagulant should be selected for specific water quality characteristics, the water should be mixed or agitated, and there should be adequate contact time between the coagulant and water (Kweinor Tetteh et al., 2017). Including regular monitoring and controlling water quality parameters and treatment process performance. Since the post chlorination stage serves as a preventative precaution against recontamination as well as the last stage in EC and bacteria removal (Albinana-Gimenez et al., 2009). In order to comply with drinking water guidelines, it is necessary to maintain the residual chlorine concentration below 0.5 ppm during the chlorination treatment process (Agency, 1999).

3.5.7 Comparative assessment with Europe, Asia, and North America

The conducted comparative assessment study aimed to investigate the occurrence levels of Nevirapine, Atenolol, Sulfamethoxazole, Efavirenz, and Carbamazepine in selected drinking water treatments and water matrices across different regions. The results showed that the average concentration of these ECs varied in different regions, with South Africa (KwaZulu Natal), Asia, Europe, and North America reporting different average concentrations. The removal efficiencies of these ECs by chlorination treatment units were also found to vary across different regions, with South Africa, North America, Asia, and Europe. The data comparison is tabulated in Table 12 below.

The concentrations of Nevirapine, Atenolol, Sulfamethoxazole, Efavirenz, and Carbamazepine in selected drinking water treatments were determined in different regions.

Table 12: Comparative assessment with Europe, Asia, and North America

Emerging contaminants	Africa (South Africa)			Asia			Europe			North America		
	(ng/L)	Matrix	Removal (%)	(ng/L)	Matrix	Removal (%)	(ng/L)	Matrix	Removal (%)	(ng/L)	Matrix	Removal (%)
Nevirapine	24.08	DW	85.32	1.59	DW	24% to 95%	<30	DW	-	27.73	DW	-
sulfamethoxazole	14.67	DW	87.17	25	DW	>99	52	DW	9	71	WW	70
Carbamazepine	23.08	DW	79.94	2.3	DW	99	30	DW	88.9	79	DW	98
Atenolol	45.44	DW	76.99	690	DW	-	380	DW	96.3	40	DW	46.3
Efavirenz	21.80	DW	70.89	1521	WW	81	<20	DW	70	-	DW	-

*DW-drinking water, SW-surface water, WW- wastewater, n.r (not reported)

Sulfamethoxazole

Several studies conducted in different regions of Asia, Africa, North America, and Europe have provided information on the concentration and removal efficiency of sulfamethoxazole in drinking water. In Japan, the reported occurrence level was 0.9 ng/L, with a removal efficiency exceeding 99% (Simazaki *et al.,* 2015). Similarly, in Malaysia, the occurrence level was 25 ng/L, and the reported removal efficiency was also above 99% (Praveena *et al.,* 2018). Spain reported an occurrence level of 1 ng/L with a removal efficiency exceeding 99% (Boleda *et al.,* 2011). In Canada, the occurrence level was 0.33 ng/L, and the reported removal efficiency was greater than 66.3% (Kleywegt *et al.,* 2011). The United States (US) had an occurrence level of 0.37 ng/L, with a removal efficiency exceeding 57.5% (Subedi *et al.,* 2015). Another study based in Asia reported removal efficiencies ranging from 63% to 92.2% (Lin, Yu, and Chen 2016). Various parts of Europe, including Northern Ireland, Northern Italy, and Greece, reported sulfamethoxazole occurrence levels ranging from 10 to 52 ng/L, with removal efficiencies of 0% to 9% (Ashton, Hilton, and Thomas 2004; Loos *et al.* 2007; Straub 2016). Again, in the US, sulfamethoxazole concentrations were detected to range from 4 to 71 ng/L, and the average removal efficiency was reported to be 70% (Gevao *et al.,* 2022). In this study conducted in KwaZulu Natal, South Africa, the mean concentration of sulfamethoxazole was determined to be 14.67 ng/L, with a removal efficiency of 87.17%.

In terms of comparisons, the United States exhibited the highest level of sulfamethoxazole occurrence, whereas the highest removal efficiencies of sulfamethoxazole in drinking water were observed in Asia.

Atenolol

Numerous studies carried out in various regions including Asia, Africa, North America, and Europe have yielded valuable data regarding the concentration and removal efficiency of atenolol in drinking water. In Spain, the reported occurrence level of atenolol in drinking water was 380 ng/L, with a removal efficiency exceeding 19.1% (Huerta-Fontela *et al.,* 2011). Similarly, in France, the occurrence level was 0.4 ng/L, and the reported removal efficiency was 96.3% (Vulliet *et al.,* 2011). In the US, the occurrence level was 3.8 ng/L, with a removal efficiency exceeding 46.3% (Subedi *et al.,* 2015). In the South Korean Mankyung River, the average concentration of atenolol was 690 ng/L, but no specific removal efficiency was reported (Kim *et al*. 2009). In Germany and Switzerland, the average concentrations of atenolol in treated water were reported as 27 ng/L, respectively, with average removal efficiencies of 70%. (BLAC 2003; Castiglioni *et al.* 2006; Vieno, Tuhkanen, and Kronberg 2006; Maurer *et al.* 2007; Vieno *et al.* 2007). In the US, the average concentration of atenolol detected was 40 ng/L, but no specific removal efficiency was reported (Kim *et al*., 2007; Organization, 2012). In this study, the mean concentration of atenolol was found to be 45.43 ng/L, with a removal efficiency of 76.99%. When comparing different regions, it was found that Asia showed the highest occurrence of atenolol, whereas Europe demonstrated the highest removal efficiencies of atenolol in drinking water.

Carbamazepine

Multiple studies conducted across diverse regions such as Asia, Africa, North America, and Europe have contributed significant insights into the concentration and removal efficiency of carbamazepine in drinking water. In Japan, the reported occurrence level of carbamazepine in drinking water was 0.4 ng/L, with a removal efficiency exceeding 99% (Simazaki *et al.,* 2015). Similarly, in China, the occurrence level was 2.3 ng/L, and the reported removal efficiency was also above 99% (Wu *et al.,* 2015). In Spain, the occurrence level of carbamazepine was reported as 1.1 ng/L, with a removal efficiency exceeding 99% (Huerta-Fontela *et al.,* 2011).

Another study reported a high removal efficiency of 98% for carbamazepine in North America (Simazaki *et al.* 2015). Across different regions of Europe, the average occurrence level of carbamazepine in treated water was 30 ng/L, with a maximum reported removal efficiency of 88.9% (van Stee *et al.* 2002; Tixier *et al.* 2003; Ashton, Hilton, and Thomas 2004; Weigel, Kallenborn, and Hühnerfuss 2004; Osenbrück *et al*. 2007; Devault *et al.* 2021). In the US, the average concentration of carbamazepine detected was 79 ng/L, and the reported removal efficiency was 94% (Brun *et al.,* 2006; Kim *et al.,* 2007). In this study conducted in KwaZulu Natal, South Africa, carbamazepine had an average concentration of 23.80 ng/L and a removal efficiency of 79.94%. When analyzing the data from the four continents, it was observed that North America exhibited the highest occurrence of carbamazepine, while Asia demonstrated the highest removal efficiencies of this compound.

Nevirapine

Several studies conducted in different regions of Asia, Africa, North America, and Europe have provided information on the concentration and removal efficiency of nevirapine in drinking water. In Guangdong province, China, one study reported an average concentration of 1.59 ng/L, with a removal efficiency ranging from 24% to 95% (Yao *et al.,* 2021). In Germany, the average concentrations of nevirapine were reported to be < 30 ng/L, and the reported removal efficiencies were 0% (Yao *et al*., 2021; Aminot *et al*., 2015). In the USA, a study reported a nevirapine occurrence level of 27.73 ng/L in drinking water, and the reported removal efficiency was 0% (Fisher *et al.,* 2016). However, in this study, which was conducted in KwaZulu Natal, South Africa, the mean concentration of nevirapine was found to be 24.08 ng/L, with a removal efficiency of 85.32%. The data analysis of four continents revealed that KwaZulu-Natal, South Africa, displayed the highest prevalence of nevirapine, along with the most effective removal rates for this compound.

Efavirenz

Several research studies conducted across various regions in Asia, Africa, North America, and Europe have yielded valuable insights into the concentration levels and efficacy of efavirenz removal in drinking water. There was no specific information about efavirenz detected in Asian drinking water.

Though, based on the study conducted by Yao *et al.* (2021), the concentration of efavirenz in wastewater treatment plants in Guangdong province, China, was measured to be 1521 ng/L, the study also reported an 81% removal efficiency for efavirenz in the treatment process. Similarly, in Germany, the average concentrations of Efavirenz were < 20 ng/L, and the reported removal efficiencies were 0% (Yao *et al.,* 2021). On the other hand, there is currently no available information regarding the concentration and removal efficiency of Efavirenz in drinking water in the United States. In this study conducted in KwaZulu Natal, South Africa, the mean concentration of efavirenz was found to be 21.80 ng/L, with a removal efficiency of 70.89% (Yao *et al.,* 2021). When comparing the results across the four continents, Africa (South Africa) exhibited the highest occurrence and removal efficiencies of Efavirenz.

3.5.8 Conclusion

A study was conducted in KwaZulu-Natal province, South Africa to generate a database of occurrence levels and removal efficiencies of five key ECs: Nevirapine, Efavirenz, Sulfamethoxazole, Atenolol, and Carbamazepine in selected drinking water treatment plants. The study identified that SPE conditions at pH 3 were optimal for the extraction of the selected ECs, with an average of 64% SPE recovery between all selected ECs. Among the four treatment units, the chlorination treatment unit exhibited the highest removal rate, with the highest median ECs removal rate. It is also recommended that Nevirapine levels in drinking water supply need to be continuously monitored and further reduced for the benefit of toddler's health. Carbamazepine was identified as the most common EC found in water bodies and drinking water globally, with the highest occurrence in European water bodies, according to the observation and comparison made. In conclusion, the study highlighted the importance of monitoring and reducing the occurrence of ECs in drinking water sources and further research into their potential health risks. The findings of this study can be used to inform the development of more effective water treatment strategies and policies to ensure the provision of safe drinking water to communities.

Chapter 4: Kinetics, Optimal Operational Parameters in the Effective Removal of Antiretroviral Drugs (Nevirapine and Efavirenz) from Drinking Water through Chlorination: An Assessment

4.1. Introduction

In recent years, emerging contaminants (ECs), including antiretrovirals (ARVs), such as nevirapine (NVP) and efavirenz (EFV), have been detected in surface waters and wastewater, posing human and aquatic health risks (Wood *et al*., 2015; Gani *et al.,* 2021). These ARVs are widely used to combat HIV and AIDS and are released into domestic wastewater due to partial metabolism in the human body. Their presence can lead to the development of drug-resistant viruses and harm aquatic life. NVP and EFV, both non-nucleoside reverse transcriptase inhibitors, are prevalent in surface water and wastewater, primarily in sub-Saharan African countries. Given their extensive use in Africa, it's crucial to address ARV removal during water treatment processes in developing countries (Chimukangara *et al.,* 2019). These two ARVs have received limited attention in water and wastewater treatment studies, despite their extensive use in Africa, where over 21 million people received antiretroviral therapy in 2020, representing over 60% of the region's HIV-positive population (UNAIDS, 2020). While a few studies have reported ARV occurrences in water environments in Canada, Europe, and the USA (Al Rajab *et al*., 2010; Aminot *et al.,* 2015; Fisher *et al.,* 2016; Furlong *et al.,* 2017), the majority of such occurrences have been confirmed in South Africa and Kenya, as reported by Ncube *et al.* (2018). At a 5% HIV infection rate, nevirapine levels in Kisumu, Kenya, and South Africa have been reported to be 5620 ng/L (K'oreje *et al*., 2016) and 1480 ng/L in surface water (Wood *et al.,* 2015). Efavirenz concentrations in South African rivers were 354 ng/L (Rimayi *et al*. 2018). The biological wastewater treatment processes have shown variable responses to the removal of ECs in general and ARVs, resulting in their possibility of interaction with the chlorination process and subsequent release into the surface water (Ahmed *et al*., 2021; Gani *et al.,* 2021). Surface water is the primary source of influent for drinking water treatment plants. Chlorination in the form of gaseous chlorine or hypochlorite is a common method as a tertiary treatment step in drinking water and wastewater treatment, especially with a main focus as a disinfectant for the inactivation of pathogens (Matcalf *et al*., 1991).

However, chlorine (Cl_2) also acts as a chemical oxidant that can degrade organic compounds in water and wastewater. The hydrolysis of chlorine forms hypochlorous acid (HOCl) that dissociates into hypochlorite ions (ClO^-), and the dissociation equilibrium depends on pH and temperature (equations I and II). These two species (HOCl and ClO) are important reactive species that react with organic compounds.

$$Cl_2 + H_2O \rightarrow HOCl + Cl^- + H^+ \qquad (I)$$

$$HOCl \rightleftharpoons ClO^- + H^+ \qquad (II)$$

Wood et al. (2016) investigated the toxicity of the transformation products for Nevirapine during chlorination of real water samples. The degradation products identified in their study were less toxic than the parent molecule. As a result, these results demonstrate the feasibility of chlorination as a means of removing NVP without any toxic by-product formation. However, currently, there are no studies on efavirenz to the best of our knowledge. Possibly, chlorination can remove these compounds completely or partially, and the removal will explain the occurrence of Nevirapine and Efavirenz in the discharge effluents of a wastewater treatment plant and surface water. Consequently, it is important to study how the operating conditions during the chlorination process influence the removal of ARVs. The effectiveness of chlorination depends on operating conditions such as pH, temperature, concentration of chlorine, and contact time. This study aimed to investigate the degradation efficacy and kinetics of Nevirapine and Efavirenz, considering varying pH levels, temperatures, and chlorine dosages.

4.2. Materials and methods

4.2.1 Chemicals and reagents

All chemicals and standards were purchased from Sigma Aldrich chemicals in United State of America.

4.2.2 Experimental procedures

Experiments were carried out to determine the degradation percentage for each ARV as well as the pseudo first order rate constant (K_{obs}) and apparent second order rate constant (K_{app}). Four operating factors viz., pH, temperature, initial chlorine concentration, and initial concentration during chlorination in deionized water. The experiments were conducted in 250 ml conical flasks. A benchtop pH meter was used to control and adjust the appropriate pH for each experiment. Magnetic hot plates were used to maintain the desired temperatures in the experimental flasks. Each flask containing 150 ml of deionized water was spiked with ARV at different concentrations (25, 50, 100, 150, and 200) µg/L. To assess the optimum operating parameters for ARV removal during chlorination, varying chlorine concentrations (0.2, 0.5, 1, 3, and 5) mg/L as well as pH (5.5, 6.5, 7, 7.5, and 8) and temperature (10, 15, 20, 25, and 30) °C were assessed. The experiments were conducted using deionized water. Table 24 Appendix 2 depicts the ARVs experiments under selected operational conditions. The degradation of pharmaceutical compounds is known to be induced by chlorination, and a 10-hour interval to permits a substantial observation of degradation (Collaboration, 2012). Hence, experiments were conducted for 10 hours with 2-mL aliquot samples extracted every two hours. Approximately 2 mg of ascorbic acid was added to the 2-mL aliquot samples, to quench or neutralize the chlorine (Soufan, *et al.,* 2012; Urbansky *et al.,* 2000; Land, 2005). After each ARV experiment, the samples were dried using nitrogen gas at 40 °C and then stored at -4 °C. To prepare the refrigerated samples for liquid chromatography mass spectrometer analysis, they were reconstituted with 1 mL of methanol.

4.2.3 Analytical methods

The analysis was performed using SCIEX uHPLC-MS 5500 equipped with a mass spectrometer MS, with a triple-quadrupole mass analyzer (m/z range: 0-3000; ionization modes: ESI+/-). The ultra-high performance liquid chromatography-mass (uHPLC-MS) column temperature was set at 30℃ and the injection volume was 5 µL. The analysis was performed using a non-polar Shim-pack GISS C18 column from Shimadzu, with particle size of 1.9µm, internal diameter of 2.1 mm and length of 100 mm. The optimized gradient consists of 0.1 % (v/v) formic acid in methanol and 0.1 % (v/v) formic acid in LC/MS water.

4.3. Results and discussion

4.3.1 Effect of operational parameters

4.3.1.1 pH

The investigated pH effect on Nevirapine and Efavirenz removal was examined at 25°C, with initial concentrations of 100 µg/L. The degradation trends at each pH are shown in Figure 22 a (Nevirapine) and Figure 22 b (Efavirenz).

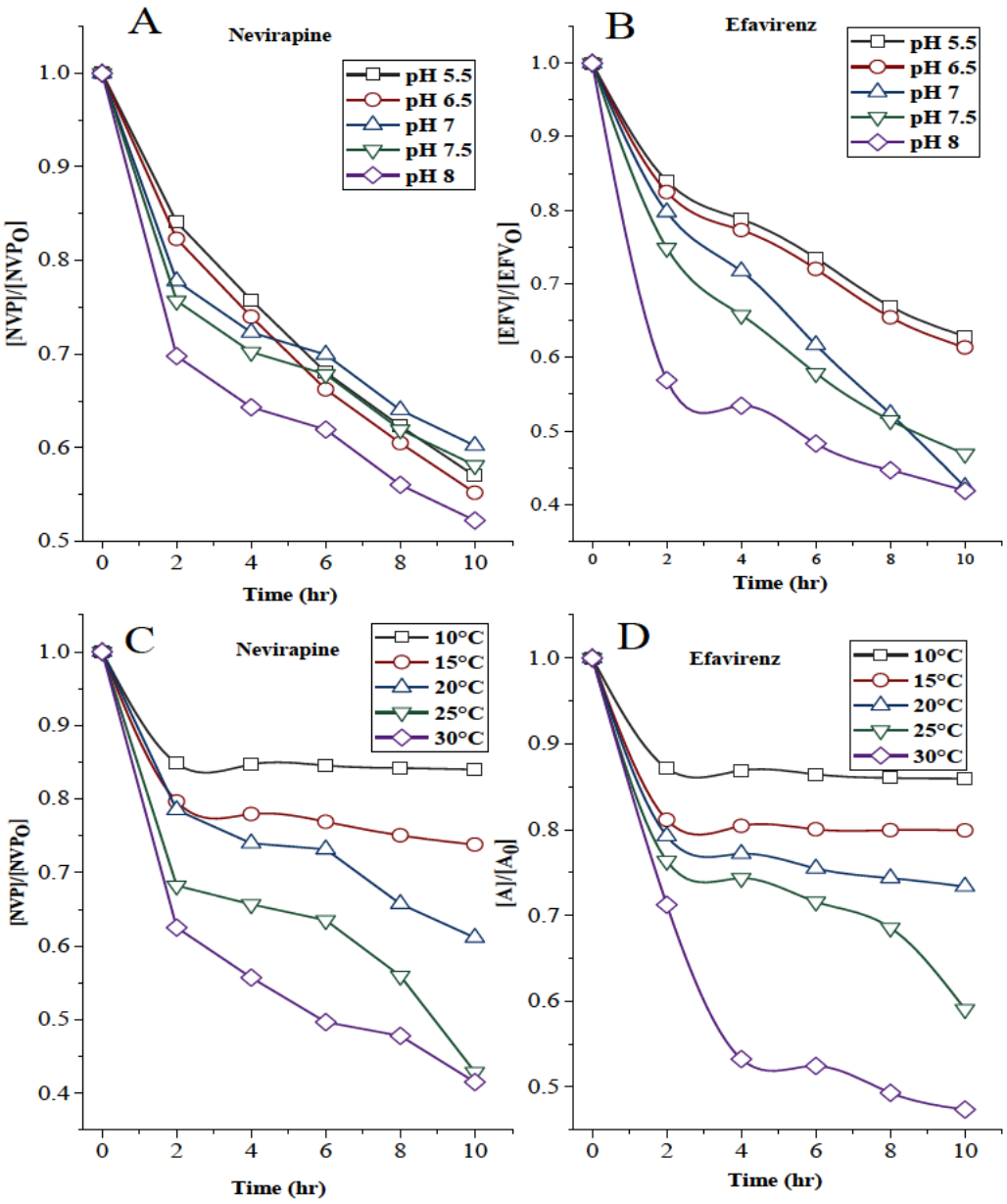


Figure 22: Degradation of the Nevirapine and Efavirenz at various pH and temperature.

The removal of efavirenz was more sensitive to the pH during chlorination. The removal of Nevirapine and Efavirenz was 43% and 37%, respectively, at pH 5.5.A pH increase from 5.5 to 7 resulted in a 40% removal of Nevirapine and a 68% removal of Efavirenz. A pH of 8 resulted in the most efficient removal of Nevirapine (48%) and Efavirenz (68%). The above results suggest that monitoring pH during chlorination plays an important role in facilitating ARV removal, which must be monitored to ensure its effectiveness. In addition, Nevirapine and Efavirenz were removed differently under similar chlorination conditions, suggesting that different ARVs may be removed more effectively at different pH levels. It can therefore be concluded that chlorination effectiveness depends on ARV properties. The effect of pH on the removal of ECs such as estrogens and few antibiotics were studied previously (Deborde *et al*., 2005; Maniero *et al*., 2008). However, the effect of chlorination on Efavirenz and Nevirapine removal at different pH has not yet been reported. At basic pH, the OCl^- species of the chlorination reaction predominates and is a weaker oxidant than HOCl. The enhanced removal of Efavirenz at higher pH may therefore be due to its speciation (i.e., anionic, cationic, or neutral) at higher pH rather than reactivity of OCl^-. Wood *et al.* (2016) reported 90% removal of Nevirapine at basic pH which was not profound in our study. Between pH 5.5 and pH 8, only 40% to 48% of the removal was observed. The difference in the results may be attributed to the higher chlorine and initial Nevirapine concentration used in the experiments by Wood *et al.* (2016). In our experiments, we used a lower concentration of nevirapine (100 µg/L) and 1 mg/L Cl_2 to study nevirapine removal at a realistic (environmental) concentration.

4.3.1.2 Temperature

The degradation of Nevirapine and Efavirenz at different temperatures is shown Figure 19 c (Nevirapine) and Figure 21 d (Efavirenz). The lowest selected temperature (10 ºC) resulted in the removal of only 16% of Nevirapine in 10 hours, while at 30 ºC, 58% of Nevirapine was removed, indicating that the increase in temperature facilitates the removal of Nevirapine during chlorination. A similar observation was made regarding the removal of Efavirenz at various temperatures. At 10 ºC, the removal of Efavirenz was 14% while at 30 ºC, the removal was increased to 53%. The Arrhenius equation (E.q.17) was used to evaluate the effect of temperature at pH 7.5 and [HClO] = 2.86×10^{-5}M.

$$\ln K_a = \frac{E_a}{RT} + \ln A \qquad (17)$$

Wherein, R represents the molar gas constant (8.314 $KJ \cdot mol^{-1}$), A represented pre-exponential factor (Dong et al., 2019), E_a is activation energy and T represents temperature (K). The relationship between ln K and 1/T was found to have a good linear correlation (R^2>0.94). The E_a of Nevirapine chlorination was 27.83 $KJ \cdot mol^{-1}$ and that of Efavirenz chlorination 21.17 $KJ \cdot mol^{-1}$. Positive activation energy means the chlorination reaction of Nevirapine and Efavirenz is endothermic. Previous studies on chlorination of ECs such as pharmaceuticals (Acero *et al*., 2013) and estrogens (Li *et al*., 2017) have reported the endothermic nature of the chlorination reaction. As reported in this study, the temperature dependency of the removal of Nevirapine and Efavirenz during chlorination may contribute to the temporal variation of these compounds in drinking water and wastewater treatment effluents.

4.3.1.3 Initial chlorine concentration

The percentage of Nevirapine removed at the initial chlorine concentration of 0.2 mg/L after 10 hours was 32%, while 97% removal was observed with the chlorine concentration of 3 mg/L and 5 mg/L (Figure 23a). Efavirenz showed comparatively significant variations in the removal while increasing the chlorine concentration from 0.2 mg/L (60% removal) to 3 mg/L (90% removal) (Figure 23b).

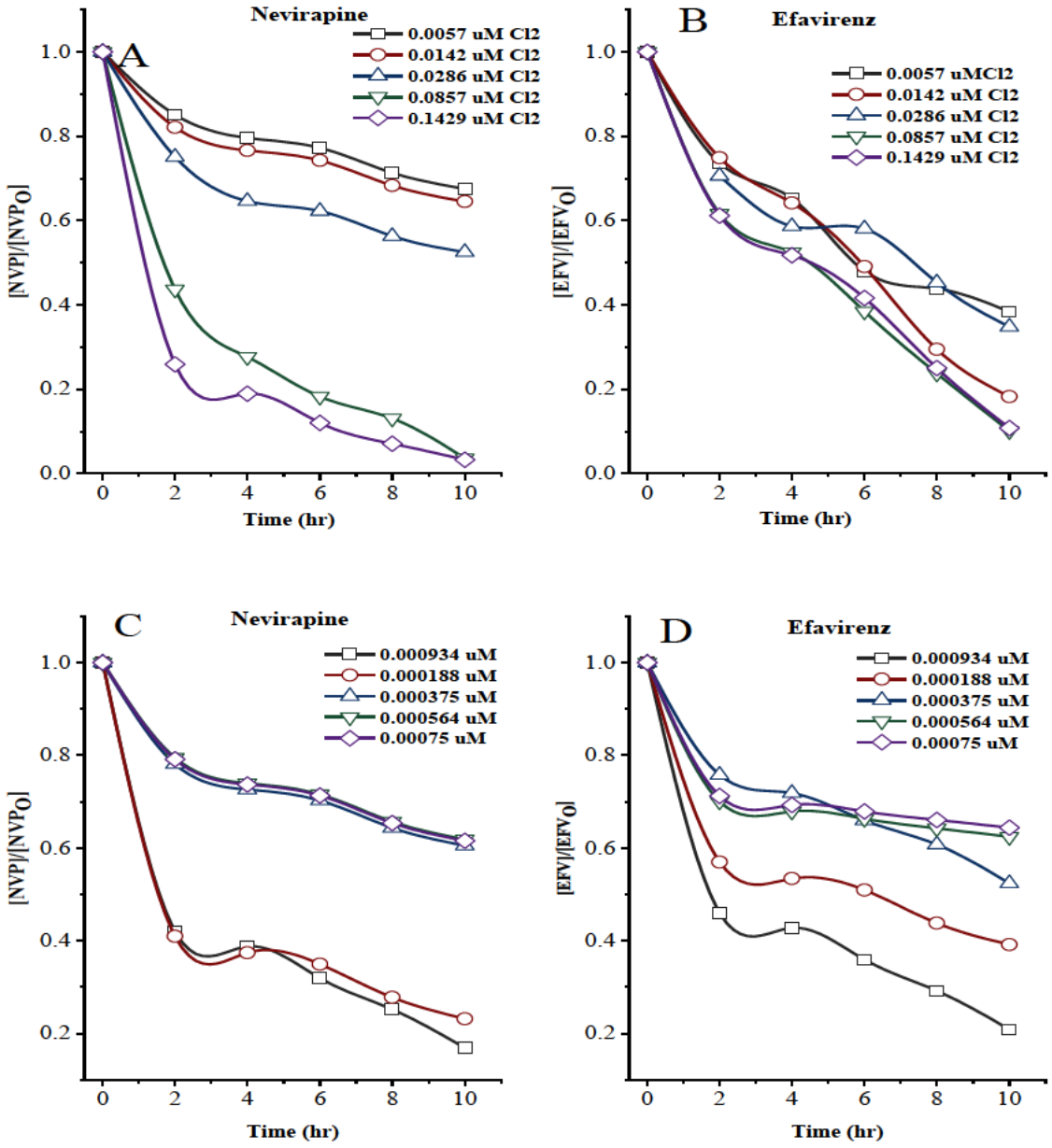


Figure 23: Degradation of the Nevirapine and Efavirenz at various initial concentration of chlorine and antiretroviral.

Although the observations of this study do not represent the actual treatment conditions where there are other reactive species that chlorine reacts with. However, the findings indicated that increase in the chlorination dosage may increase the removal of Nevirapine and Efavirenz. This study showed >90% removal of Nevirapine and Efavirenz at the chlorine concentration of 3 mg/L - 5 mg/L. However, using this much of chlorination dosages may increase in the typical free residual chlorine that may have negative implications on the water consumption by public. Therefore, there is a need of de-chlorination, if chlorination dosage is increased for removal of Nevirapine and Efavirenz.

4.3.1.4 Initial concentration of antiretroviral

The effect of initial concentration of Nevirapine and Efavirenz was investigated during chlorination. The experiments were conducted with selected initial concentration range of antiretroviral as 25 µg/L to 200 µg/L, respectively, pH 7.5, and 25ºC, initial chlorine concentration was 1mg/L and the experiment lasted for 10 hours. The removal of Nevirapine was 84% at the initial concentration of 25 µg/L while as the rem0oval was only 39% as the initial concentration of Nevirapine increased to 200 µg/L (Figure 23c). Similar results of decrease in removal with increase in the initial concentration of Efavirenz were observed. The removal of Efavirenz at 25 µg/L initial concentration was 80% and it decreased to 36% as the initial concentration of Efavirenz was increased to 200 µg/L (Figure 23d). The dependence of removal rates on the initial concentration of Nevirapine and Efavirenz may indicate that their environmental concentration in different water matrices may have implications on the removal rates by chlorination. There have been reports of variable detection frequencies and concentrations of ECs in water samples (Murray *et al*., 2010). This variation in the initial environmental concentration of the compound will influence their removal by chlorination at full scale wastewater treatment plants. Based on available literature, the reported maximum concentrations are within the range of (1480 ng /L - 17,400 ng /L) for both ARVs (Adeola and Forbes, 2022).

4.3.2 Reaction kinetics between ARVs and chlorine

The obtained K_{obs} and K_{app} values are tabulated in Table 13. The maximum K_{app} obtained for Nevirapine was 109.67 x 10 $^{-2}M^{-1.}$ s^{-1} , with experimental pH 7.5 and temperature of 25°C, and the maximum K_{app} for Efavirenz was 95.47 x 10 $^{-2}M^{-1.}$ s^{-1} , under similar pH and temperature. The K_{app} values varied in direct proportion to temperature. K_{app} increased from 1.3 x 10 $^{-2}M^{-1.}$ s^{-1} to 47 x 10 $^{-2}M^{-1.}$ s^{-1} in the case of Nevirapine and from 1.9 x 10 $^{-2}M^{-1.}$ s^{-1} to 43.4 x 10 $^{--2}M^{-1.}$ s^{-1} in the case of Efavirenz with a threefold rise in temperature from 10 ºC to 30ºC, showing a roughly 1.5 times increase in reaction rate with each unit increase in temperature. A plot of log K_{app} with pH for Nevirapine showed higher log K_{app} values between pH of 5.5 and 7 and Efavirenz showed higher log K_{app} values between pH of 7 to 8 (Figure 24). This may indicate the favorability of hypochlorous acid mediated chlorination reaction in Nevirapine as the dissociation of chlorine into hypochlorite ion and hypochlorous acid depends on solution pH and the latter ion is more available at a pH range of 5.5 and 7. Consequently, the reaction mechanism of the whole chlorination reaction depicting the reaction affinity of the Nevirapine and Efavirenz with different chlorine forms needs investigation. For this, the intrinsic reaction coefficients based on the probable ionization of the Nevirapine and Efavirenz were derived that can explain the reaction of the selected ARVs with the chlorine.

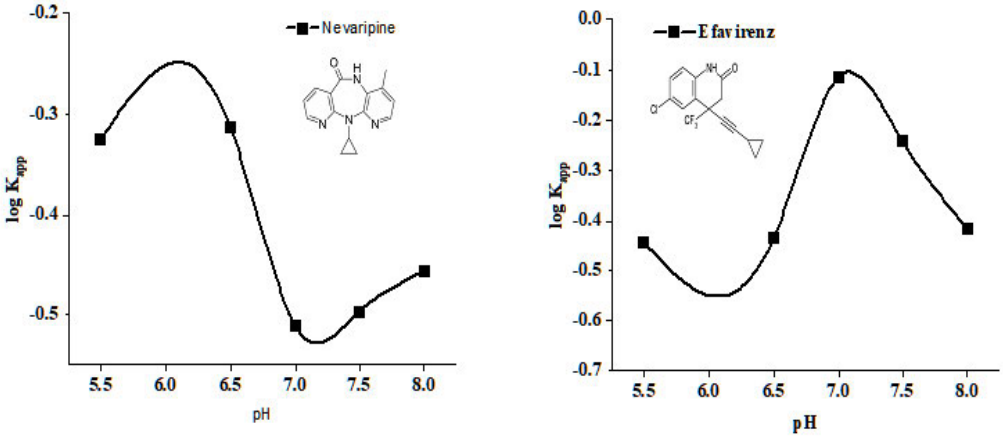


Figure 24: Variation of log K_{app} with respect to pH of the matrix for Nevirapine and Efavirenz.

Table 13: Nevirapine and Efavirenz measured K_{obs} and K_{app} values at different conditions.

				Nevirapine		Efavirenz	
Cl_2 1x 10^{-5}M	T, °C	pH	Spiking Concentration (µg/L)	K_{obs} $M^{-1}. s^{-1}$ (1 x10^{-6})	k_{app} $M^{-1}. s^{-1}$ (1 x10^{-2})	K_{obs} $M^{-1}. s^{-1}$ (1 x10^{-6})	k_{app} $M^{-1}. s^{-1}$ (1 x10-^{2})
2.86	10°C	7.5	100	0.36	1.26	0.53	1.85
2.86	15°C	7.5	100	2.64	9.24	0.5	1.75
2.86	20°C	7.5	100	8.58	30.04	2.67	9.33
2.86	25°C	7.5	100	15.14	52.98	8.81	30.82
2.86	30°C	7.5	100	13.5	47.25	12.39	43.36
2.86	25°C	5.5	100	13.5	47.34	10.31	36.07
2.86	25°C	6.5	100	13.9	48.61	10.53	36.85
2.86	25°C	7	100	8.8	30.82	21.94	76.81
2.86	25°C	7.5	100	9.08	31.79	16.42	57.46
2.86	25°C	8	100	9.97	34.9	11	38.51
2.86	25°C	7.5	25	31.33	109.67	27.28	95.47
2.86	25°C	7.5	50	19.972	69.9	13.17	46.08
2.86	25°C	7.5	100	8.78	30.72	12.56	43.94
2.86	25°C	7.5	150	8.61	30.14	3.97	13.9
2.86	25°C	7.5	200	8.634	30.23	3.47	12.15
0.57	25°C	7.5	100	7.94	139.03	23.61	413.22
1.42	25°C	7.5	100	8.28	57.94	50.05	350.38
2.86	25°C	7.5	100	11.83	41.42	23.22	81.28
8.57	25°C	7.5	100	79.58	92.85	61.31	71.53
14.29	25°C	7.5	100	71.36	49.95	58.33	40.83

4.3.3 Intrinsic chlorination rate constants

The next objective was to determine the intrinsic rate constants for the Nevirapine and Efavirenz during the chlorination processes. As a result, an overall reaction mechanism is required for the chlorination of these two selected ARVs. For this, the dissociation of ARVs into different ionized forms was proposed as equation (E.q.18) and (E.q.19), leading to the formation of three species in the chlorination reaction mixture. These species can be a neutral form of Nevirapine (N), an anionic form (N^-) or a cationic form of Nevirapine (N^+). The dissociation constants for the equilibrium conditions of equation (E.q.18) and (E.q.19) are K_{a1} and K_{a2} respectively. The equations for kinetics are mentioned assuming Nevirapine is a representative compound, and these are applicable to Efavirenz.

$$N^+ \overset{K_{a1}}{\leftrightharpoons} N + H^+ \qquad (18)$$

$$N \overset{K_{a2}}{\leftrightharpoons} N^- + H^+ \qquad (19)$$

Similarly, the possible ionized species of Efavirenz can be neutral (E), and cationic form (E^+). As discussed, the reaction of Nevirapine and Efavirenz with hypochlorous acid is dominating; therefore, the reaction of the various species of Nevirapine and Efavirenz with hypochlorous acid (HOCl) was considered. The other reason for not considering the reactions of OCl^- ion with the species of Nevirapine and Efavirenz is its low reactivity (Deborde and Gunten, 2008). The pK_a of dissociation of HOCl according to equation (E.q.20) is 7.54 and the reaction of Nevirapine and Efavirenz with HOCl can be written as

$$HOCl \leftrightharpoons H^+ + ClO^- \qquad (20)$$

$$N^+ + HOCl \overset{k1}{\longrightarrow} \text{Reaction products} \qquad (21)$$

$$N + HOCl \overset{k2}{\rightarrow} \text{Reaction products} \qquad (22)$$

$$N^- + HOCl \overset{k3}{\rightarrow} \text{Reaction products} \qquad (23)$$

In the case of Efavirenz, since only two species (E and E^+) exist, equation (E.q.23) is not valid. The reaction of HOCl with each ARV under the influence of hydrogen ions is also possible and can be written as equation (E.q.24).

$$N^+ + HOCl + H^+ \xrightarrow{k_c} \text{products} \qquad (24)$$

Combining all reactions, the whole chlorination reaction of the ARVs can be described by the equation (E.q.25).

$$\frac{d[N]}{dt} = k_1[HOCl][N^+] + k_2[HOCl][N] + k_3[HOCl][N^-] + k_c[N^+][HOCl][H^+] \qquad (25)$$

Equating equation (E.q.25) with equation (E.q.7) and substituting the species of ARVs from equations E.q.18 and E.q.19, the solution in terms of estimated K_{app} for Nevirapine and Efavirenz can be represented by equation (E.q.26) and (E.q.27) (Acero *et al.*, 2013).

$$K_{app} = \frac{\{k_1[H^+]^2 + K_{a1}k_2[H^+] + k_3K_{a1}K_{a2} + k_c[H^+]^3\}\left\{\frac{[H^+]}{[H^+] + K_{HOCl}}\right\}}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}} \qquad (26)$$

$$K_{app} = \frac{\{k_1[H^+] + K_{a1}k_2 + k_c[H^+]^2\}\left\{\frac{[H^+]}{[H^+] + K_{HOCl}}\right\}}{[H^+] + K_{a1}} \qquad (27)$$

The $[H^+]$ concentration at each experiment was obtained from the pH value and the corresponding measured K_{app} values from Table 13 were used to obtain solutions of equations 26 and 27 by non-linear regression analysis. The solutions gave intrinsic rate constants (k_1, k_2, k_3, k_c) for Nevirapine and Efavirenz (k_1, k_2, and k_c), as shown in Table 14. The estimated K_{app} value was plotted against measured K_{app} values in Figure 25, which showed a good agreement indicating the validation of the probable chlorination reactions, represented by equation (E.q.26) to (E.q.27). The intrinsic rate constant of the protonated reaction of HOCl equation (E.q.27) was substantial for both compounds (Table 14). This may be attributed to the fact that Efavirenz and Nevirapine contain a tertiary amine, a functional group that readily interacts with chlorine (Prütz, 1998); (Mitch and Schreiber 2008). The HOCl would then deprotonate the tertiary amine in both ARVs during disinfection with sodium hypochlorite (NaOCl) in deionized water. Hence, the reaction would then form a chlorammonuim cation, also producing more nucleophilic species at optimum conditions of high ARV degradation (Isaza Ferro et al., 2021). The cyclopropane functional group in both Efavirenz and Nevirapine also underwent further hydrolysis, speeding up the breakdown of the selected ARVs (Wood et al., 2016).

Table 14: Intrinsic rate constants for the chlorination of each species

Antiretroviral drugs	k_1 $M^{-1}. s^{-1}$	k_2 $M^{-1}. s^{-1}$	k_3 $M^{-1}. s^{-1}$	k_c $M^{-1}. s^{-1}$
Nevirapine	9.1×10^{-3}	0.451	0.56	737.3
Efavirenz	0.58	200	-	512.6

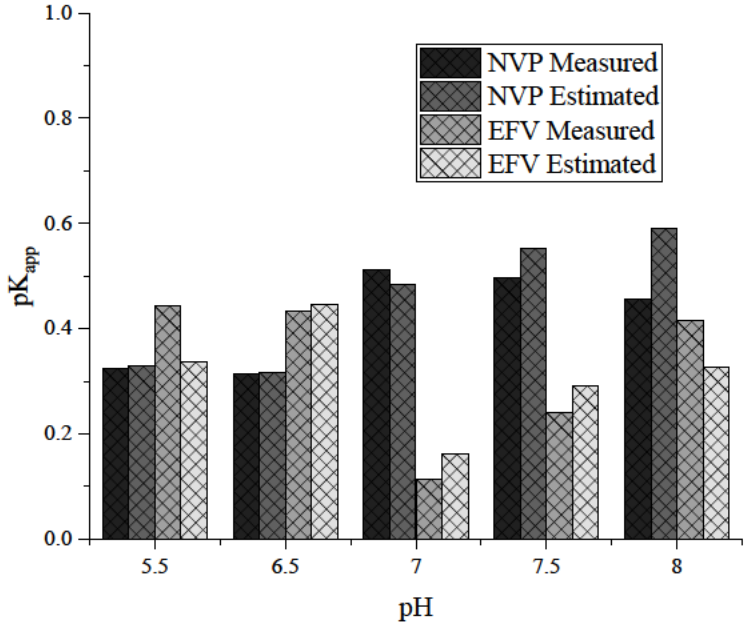


Figure 25: Comparison of measured pK_{app} with pK_{app} values estimated from the proposed chlorination reactions and derived intrinsic rate coefficients.

4.3.4 Chlorination efficacy in conventional treatment systems

After calculating the K_{app} values at various conditions, as discussed in previous sections, the half-life of Nevirapine and Efavirenz was estimated with respect to various pH and temperature and chlorine dosages that are often used at treatment plants. The chlorine concentrations used were 0.5 mg/L, 1mg/L and 2 mg/L, typical concentrations used in primary and secondary disinfection (Metcalf *et al*., 1991).

The half-life results are shown in Figure 26 The half-life of Nevirapine at pH range from 5.5 to 8 was minimum (0.3 days for Cl_2 concentration of 2mg/L) at pH <7 and decreased with an increase in chlorine concentration. However, for Efavirenz, the minimum half-life was 0.1 days (chlorine concentration 2mg/L) at pH 7. These long half-lives of ARVs indicate that treatment systems may not be able to remove these compounds due to such elongated periods. However, the dependence of half-lives with pH also indicates that acidic wastewater matrices can be favourable for the degradation of Nevirapine. Notably, when the temperature was set to 10°C, the resulting half-life values exhibited an unrealistic range of durations, extending from 125 to 2000 days. However, a subsequent elevation of the temperature to 30°C yielded more realistic half-life values, ranging from 0.1 to 2.3 days. These temperature dependence of half-life of Nevirapine were comparatively smaller (11-45 days at temperature of 10°C. These results suggest that chlorination may be useful for removing ECs in hot regions, provided that the chlorination contact chambers are designed to support such long periods of operation.

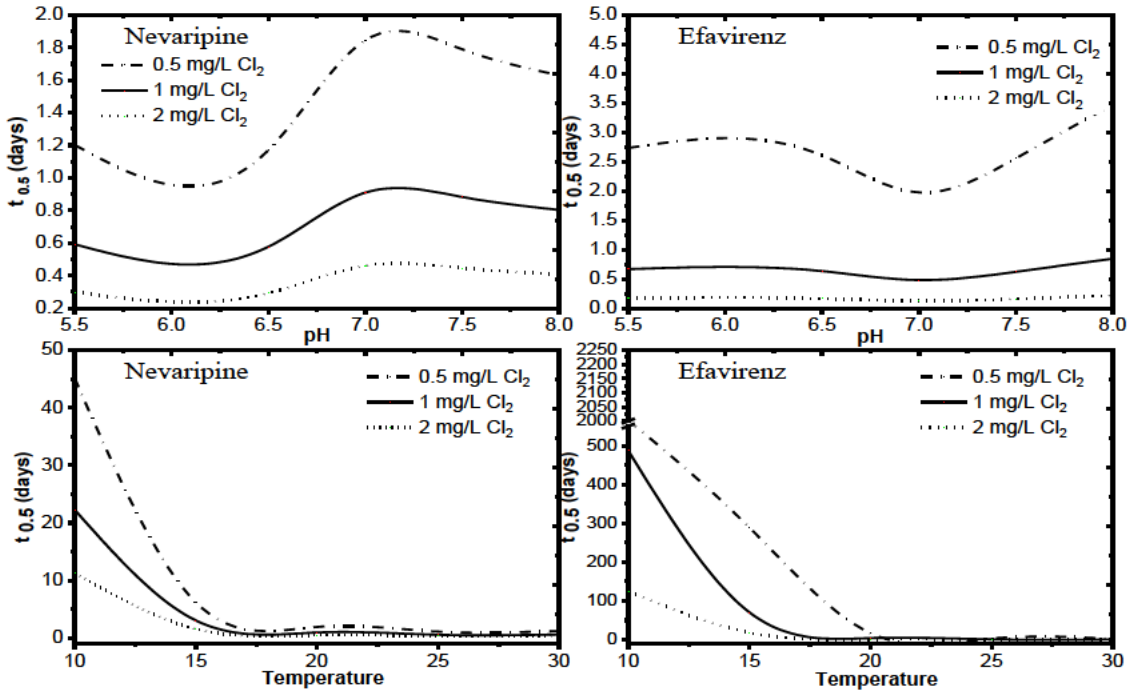


Figure 26:Half-life of Nevirapine and Efavirenz at different pH and temperatures under chlorine dosages used at conventional treatment conditions.

4.3.5 Exposure time and HRTs for chlorination of ARVs

Contact time (CT) is suitable for assessing degradation in batch reactor experiments when residual chlorine interacts with the emerging synthetic or natural contaminant present in the water matrix. Hence, the equation (E.q.28) can be used for the evaluation of contact time for Nevirapine and Efavirenz for a plug-flow reactor (PFR), where the hydraulic residence time (HRT) must be considered rather than the reaction time. However, in drinking water treatment, full-scale reactors follow a non-ideal flow model, which can be assumed of as a continuous stirred tank reactor model (CSTR) (Acero et al., 2010). Therefore, the expression provided for evaluating the CT required for PFR and CSTR are in equation (E.q.28) and (E.q.29).

$$CT = -\frac{\ln\left(\frac{[A]}{[A_0]}\right)}{K_{app}} \qquad (21)$$

$$CT = \frac{\left(\frac{[A_0]}{[A]}\right) - 1}{K_{app}} \qquad (22)$$

The apparent second order constant K_{app} values in Table 13 were used to compute CT for 99% removal of Nevirapine and Efavirenz in PFR and CSTR. The exposure values calculated were very high especially at lower temperatures (10^{o}C) for both Nevirapine and Efavirenz and depicted in Table 15. However, CSTRs type reactor configuration showed lower exposure values indicating a CSTR may be a better choice for the removal of Nevirapine and Efavirenz by chlorination, reducing the exposure coefficients by an average of 27%. The hydraulic retention time (HRT) of chlorination tanks for a 99% removal of Nevirapine and Efavirenz using a chlorine dosage of 2mg/L was estimated (Table 15). The HRT for a CSTR was lower than the PFR and the estimated HRT for a CSTR was feasible value. The minimum HRT for Nevirapine was 1.56 hours (pH 7.5 and temperature of 25^{o}C) for Efavirenz and 1.07 hours (pH 7and temperature of 25^{o}C). HRT will influence the volume of the chlorination reactors at water treatment plants. The variation of HRT values, as illustrated in Table 16, emphasizes the substantial influence exerted by different operational conditions on the sizing of chlorination chambers.

Further, the estimated HRT in the range of 1-2 hours indicates that chlorination may be an applicable process for removing Nevirapine and Efavirenz in drinking water treatment plants. These results, although they do not represent the actual field conditions, indicate that operating factors, reactor type, and size can affect the removal efficiency of these compounds during chlorination in drinking water and wastewater treatment systems.

Table 15: Estimated exposure values in terms of CT (mg min/L) for 99% removal of Nevirapine and Efavirenz by chlorination

T, °C	pH	CT (mg min/L)			
		Plug flow reactor		Continuous stirred tank Reactor	
		Nevirapine	Efavirenz	Nevirapine	Efavirenz
10°C	7.5	$2.1x10^5$	$1.6 x10^5$	7832	5359
15°C	7.5	$0.29 x10^5$	$1.5 x10^5$	1072	5657
20°C	7.5	8942	28782	330	1061
25°C	7.5	5070	8716	187	321
30°C	7.5	5685	6195	210	228
25°C	5.5	5674	7448	209	275
25°C	6.5	5526	7290	204	269
25°C	7	8716	3498	321	129
25°C	7.5	8450	4675	312	173
25°C	8	7697	6977	284	257

Table 16: Estimated hydraulic retention time in chlorination chambers for 99% removal of Nevirapine and Efavirenz by chlorination dosage of 2mg/L.

T, °C	pH	HRT (hours)			
		Plug flow reactor		Continuous stirred tank Reactor	
		Nevirapine	Efavirenz	Nevirapine	Efavirenz
10°C	7.5	1771	1212	65	45
15°C	7.5	242	1279	9	47
20°C	7.5	74	240	3	9
25°C	7.5	42	73	1.6	2.7
30°C	7.5	47	52	1.8	1.9
25°C	5.5	47	62	1.7	2.3
25°C	6.5	46	61	1.7	2.2
25°C	7	73	29	2.7	1.1
25°C	7.5	70	39	2.6	1.4
25°C	8	644	58	2.4	2.1

4.4 Conclusions

This study investigated the effectiveness of chlorination in removing Nevirapine and Efavirenz and its kinetics. It was demonstrated that chlorination under specific operational conditions (pH, temperature, chlorine dosage) could effectively remove Nevirapine and Efavirenz from water. Chlorination emerges as a cost-effective method for the removal of ARVs from water, as observed in various studies. The effectiveness of this method is influenced by factors such as pH, temperature, and chlorine concentration, which play a significant role in the removal of Nevirapine and Efavirenz. The observed variations in the concentrations of these compounds in wastewater treatment plant effluents can be attributed to the effects of pH, temperature, and chlorine concentration on their removal efficiency. The chlorination process demonstrated a higher removal efficiency for efavirenz at basic pH levels. The pseudo second-order rate constants were determined to estimate crucial parameters such as the half-life and HRT of the chlorination process. The estimated HRT for both ARVs was within the practical limits of 1-2 hours, considering a continuous stirred-tank reactor configuration and a chlorine dose of 2 mg/L.

Under ideal conditions of pH 7.5, a temperature of 30°C, and a chlorine dosage exceeding 2 mg/L, the removal of nevirapine reached 97%, while efavirenz was removed by 90%. The maximum K_{app} value achieved for Nevirapine was 109.67 x 10^{-2} $M^{-1} \cdot s^{-1}$, obtained at an experimental pH of 7.5 and a temperature of 25°C. Similarly, for Efavirenz, the maximum K_{app} value recorded was 95.47 x 10^{-2} $M^{-1} \cdot s^{-1}$ under the same pH and temperature conditions. The study can broadly assist to evaluate the application of chlorination for the removal of Nevirapine and Efavirenz from water and wastewater, as the process being cost effective for the developing countries such as South Africa where large-scale implementation of sophisticated advanced oxidation processes is not economically affordable.

Chapter 5: Kinetics and Trihalomethane Formation in the Chlorination-Based Removal of Antiretroviral Drugs from Drinking Water

5.1 Introduction

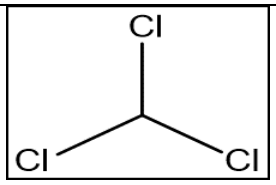
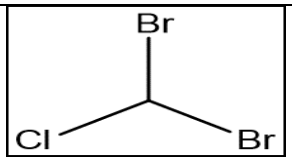
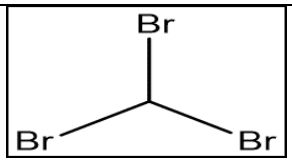
Nevirapine and Efavirenz are two widely used antiretroviral (ARV) drugs that are highly effective in managing human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) (Dubé et al., 2003). However, there is a potential risk associated with their unregulated disposal in water bodies. These ARV drugs have been observed to be susceptible to degradation when exposed to chlorine, which is a common disinfectant used to treat water. During the disinfectant treatment of drinking water, chlorination would attack the carbon-hydrogen (C-H) bonds in organic matter, particularly in compounds such as humic and fulvic acids found in natural water sources (Huang et al., 2004). As a result, Trihalomethane (THMs) and Halo acetic acid (HAA) are formed as disinfection by-products (DBPs) (Singer, 1999). Common THMs are formed when the following functional groups (ketone or aldehyde) of organic matter existing in drinking water interact with residual chlorine via substitution, heterogeneously catalyzed addition, elimination, or bromination reactions (Knight et al., 2010).The THMs formed during chlorination can vary depending on several factors, such as the type and amount of organic matter, pH, temperature, and chlorine dosage. During water chlorination, THMs account for 5-20% of the chlorinated products (Golfinopoulos and Arhonditsis, 2002). The HAAs are widespread environmental contaminants with a low evaporation tendency and high affinity for water, making them susceptible to contamination by precipitation and aerosol absorption. Dry precipitation can also contribute to HAA contamination (Hanson and Solomon, 2004). These DBPs are a group of water contaminants that can pose a health risk if consumed in high concentrations over a long period of time(Van Leeuwen, 2000). The composition and amount of DBPs present in drinking water are affected by several factors, such as the disinfectant used, the chemical and physical properties of the source water, the operational conditions of the treatment plant, the temperature of the water, and the time that the water spends in the distribution system (Marais et al., 2018).

There are six most common HAAs, namely monochloroacetic acid (MCA), dichloroacetic acid (DCA), trichloroacetic acid (TCA), monobromoacetic acid (MBA), dibromoacetic acid (DBA), tribromoacetic acid (TBA)(Malliarou et al., 2005).Though there are current methods to try and mitigate the level of DBPs in drinking water, the common first step is to control the amount of organic matter in the source water. According to the (United States Enviromental Protection Agency, 2017), the maximum contamination limit (MCLs) for total THMs in USA drinking water is 80 parts per billion (ppb) and, individual concentration limits for each of the four categories of THMs are as follows: bromodichloromethane (60µg/L) and dibromochloromethane (60 µg/L), bromoform (80 µg/L), and chloroform (70 µg/L). According to (Gan et al., 2013), the reported occurrence level of THMs present in China drinking water was 17.7 µg/L and the average HAA concentration reported was 241 µg/L (Zhao et al., 2020). In Iran, due to the high occurrences of THMs, TCM concentration value (300 µg/L) was found to be adverse (Dobaradaran et al., 2020). (Water, 2008) reported, occurrence level of THMs reported in South Africa's drinking water was 25 µg/L. According to (Lee et al., 2013), in Seoul, Korea reported the MCL of HAAs was 80 µg/L. The THMs and HAAs are harmful disinfection by-products that can pose significant risks to human health and the environment (Chowdhury et al., 2011). According to (Dietrich and Burlingame, 2015), set MCL is necessary for these DBPs in drinking water to ensure that their concentrations remain within safe limits. Removing DBPs from drinking water is important to protect public health, comply with regulations, improve the taste and odour of water, and safeguard the environment. However, there is very little information available about the levels of both THMs and HAAs in South African drinking water. This study was conducted to assess the levels of THMs in tap water during the degradation of Nevirapine and Efavirenz by chlorination. The study was performed in a laboratory setting using tap water and incorporated the reported environmental concentrations of the selected ECs. This study is important to raise awareness of the potential risks associated with Nevirapine and Efavirenz and minimize THMs in the water supply. Additionally, it was important to predict the degradation pathways of these ARV drugs and the treatment of water to better understand any potential risks.

5.2 Materials and methods

The investigation employed the same materials that were utilized in Section 4.2.2. Table 17 lists the investigated trihalomethanes in the study.

Table 17: Investigated Trihalomethanes in the Study

Name of selected Trihalomethane	Chemical Structure	Molecular weight
Chloroform		**119,38 g/mol**
Dibromochloromethane		**208,28 g/mol**
bromoform		**252,73 g/mol**

5.2.1 Experimental procedure

Experiments were carried out to determine the formation of trihalomethane, namely chloroform ($CHCl_3$), dibromochloromethane ($CHBr_2Cl$), and bromoform ($CHBr_3$) during the degradation of Nevirapine and Efavirenz by chlorination, including pseudo-first-order rate constants (K_{obs}) and apparent second-order rate constants (K_{app}). The experiments were conducted in 250 ml conical flasks. A benchtop pH meter was used to control and adjust the appropriate pH for each experiment. Magnetic hot plates were used to maintain the desired temperatures in the experimental flasks. The optimum operational parameters that achieved removal rates of over 90% for both ARVs (Chapter 5) were used for assessing the DBP formation. The degradation of ECs is known to be induced by chlorination, and a 10-hour interval permits a substantial observation of degradation (Collaboration, 2012). Hence, experiments were conducted for 10 hours with 2-mL aliquot samples extracted every two hours. Approximately 2 mg of ascorbic acid was added to the 2-mL aliquot samples, to quench or neutralize the chlorine (Soufan*, et al.,* 2012; Urbansky *et al.,* 2000; Land, 2005). After the experiments, the THM samples were promptly stored at -4 °C for further analysis.

5.2.3 Solid phase micro extraction (SPME) sample preparation

Five milliliters of samples were transferred into a 20 ml solid phase micro-extraction (SPME) vial. A 3 ml of a 20% sodium chloride (NaCl) solution was added to the vial with the sample and then vortexed for 2-4 minutes. The samples were analyzed by a 100µm Polydimethylsiloxane (PDMS) solid phase micro-extraction (SPME) fiber. The SPME vial with the sample was equilibrated for 10 minutes at 60°C in the auto sampler incubator, shaken at 250 rpm. Subsequently, a 100µm PDMS-coated fibre was exposed to the sample headspace for 20 min at 60°C. After extraction, desorption of the THMs from the fibre coating was carried out by desorption in the injection port of the gas chromatography-mass spectrometry (GC-MS) for 1 min. The fibre was conditioned for 10 minutes between the samples to avoid cross-contamination.

5.2.4 Analytical methods

Analysis was performed on a Thermo Scientific TRACETM 1310 gas chromatograph automated injection coupled to TSQ 8000 MS/MS Triple Quadrupole operated in a selected reaction monitoring (SRM) mode. Chromatographic separation of the compounds was performed on a non-polar ZB-5MSi (30 m, 0.25 mm ID, 0.25 µm film thickness) Zebron capillary column. Helium was used as the carrier gas at a flow rate of 1 ml/min. The injector temperature was maintained at 250°C operated in a splitless mode. The oven temperature was programmed as follows: 35 °C for 5 min, ramped to 120°C at a rate of 15°C/min for 0 minutes; followed by a ramping rate of 20°C/min for 5 min until 250°C. The ionization source temperature was set at 250 °C and emission current of 50 µA was used with Argon collision. The trihalomethane elution calibration curve consists of several compounds, namely chloroform, dibromochloromethane, and bromoform. These compounds are specifically presented in Appendix 3, located between Figures 31 and 33. Figure 31 illustrates chloroform, Figure 32 represents dibromochloromethane, and Figure 33 showcases bromoform. For the standard protocols of trihalomethane analysis, including the limits of detection and quantification depicted in Tables 21, 22, and 23, respectively.

5.3 Results and Discussion

5.3.1 Trihalomethanes formation

Trihalomethanes are utilized as a representation to routinely monitor and control disinfection by-products in drinking water distribution systems in the United States and Canada (Cotruvo and Amato, 2019, Chowdhury, 2018). In SA, metropolitan drinking water treatment plants conduct routine analyses of various trihalomethanes (THMs) to comply with national regulations. Notably, chloroform ($CHCl_3$), dibromochloromethane ($CHBr_2Cl$) and bromoform ($CHBr_3$) are among the predominant THMs (Mashau et al., 2021). Mitigating the presence of potential carcinogens is vital for safeguarding the health of South Africans, specifically addressing fertility issues in women and reproductive complications in both men and women (Richardson et al., 2007). On average, individuals in South Africa consume approximately 38.87 µg/day and 0.59 µg/day of THMs through their total daily intake and water ingestion (Mashau *et al.,* 2021), respectively. The South African National Standards have set a maximum contaminant level (MCL) of 300 µg/L for total THMs in tap water (SANS, 2015). Ensuring that the occurrence of these THMs does not exceed the specified threshold is crucial for the well-being of the population. In this study, three specific THMs formations were studied, namely chloroform $CHCl_3$, dibromochloromethane $CHBr_2Cl$ and bromoform $CHBr_3$. The degradation of both antiretroviral drugs, nevirapine and efavirenz, in tap water by chlorination, was evaluated for the formation of the selected THM. Figure 27 below illustrates the relationship between the formations of THMs versus time during chlorination. Before the chlorination experiments were conducted on the degradation of Nevirapine and Efavirenz in tap water, $CHCl_3$, $CHBr_2Cl$, and $CHBr_3$ were already present in tap water at concentrations of 0.39, 0.60, and 0.27 µg/L, respectively. By extrapolating the optimal operational parameters that achieved >90% removal rates for both Efavirenz and Nevirapine during chlorination from Chapter 4, the formation of trihalomethanes was assessed with the same parameters. To eliminate the initial concentrations of the three THMs prior to the spiking of the ARVs, the THM concentrations obtained from the degradation of Nevirapine and Efavirenz at every selected time interval during a period of 10 hours were subtracted from the initial three THM concentrations present in tap water. After the chlorination stage, the average formations observed for $CHCl_3$, $CHBr_2Cl$, and $CHBr_3$ were 63.49 µg/L, 25.83 µg/L, and 11.94 µg/L, respectively. Hence, the THMs analyzed displayed an average increase of >98% in THM formation.

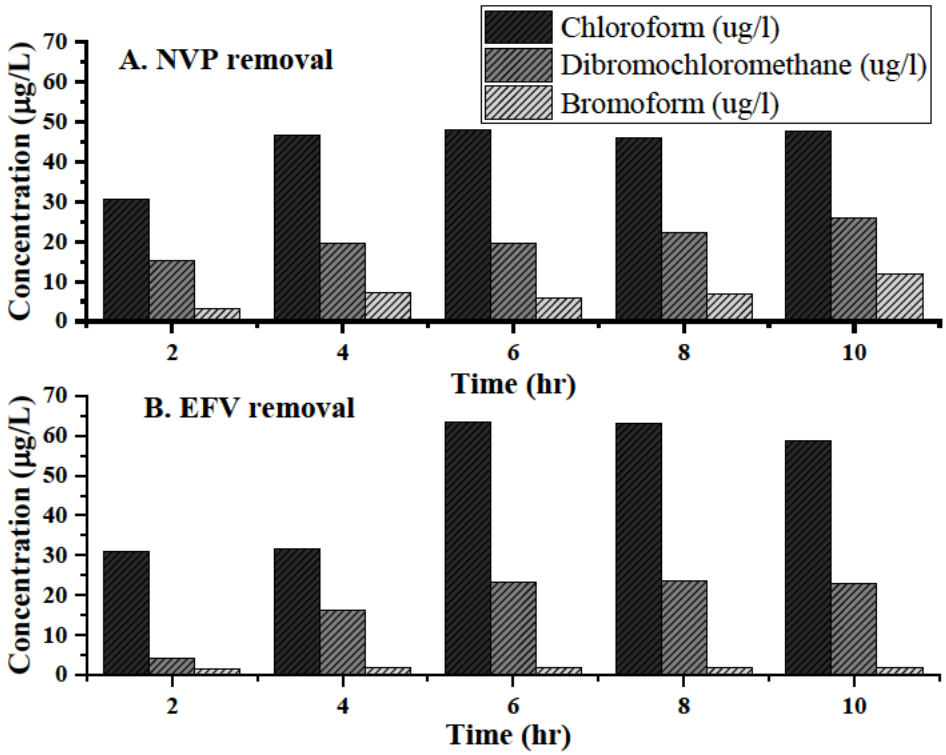


Figure 27: Formation of THMs during the degradation of (a) NVP and (b) EFV by chlorination; operational parameter: pH 7.5, Cl_2 (5ppm), at 25°C,

During the chlorination process, the degradation of nevirapine and efavirenz resulted in the formation of three predominant trihalomethanes in tap water. The formation of these selected trihalomethanes is discussed in an orderly manner: $CHCl_3$, followed by $CHBr_2Cl$, and finally $CHBr_3$. Distinct changes in $CHCl_3$ formation were observed over a 10-hour period in both experiments. In the nevirapine degradation experiment, the average formation of $CHCl_3$ was determined to be 46.86 µg/L. Conversely, during the degradation of efavirenz, the average formation of $CHCl_3$ was higher, with a value of 63.49 µg/L. When comparing the formation of $CHCl_3$ between nevirapine and efavirenz degradation, it was found that efavirenz exhibited a 26% higher yield of $CHCl_3$ compared to nevirapine.

It may be possible that efavirenz degradation produced intermediate compounds that were more readily chlorinated to form $CHCl_3$ compared to the intermediates produced during nevirapine degradation (Singh *et al.*, 2011). These intermediates may serve as precursors for $CHCl_3$ formation and could explain the observed difference in yields.

The use of 5mg/l chlorine dosage effectively removed Efavirenz, achieving a >90% removal rate. However, it led to a significant formation of > 99% $CHCl_3$. $CHBr_2Cl$ was the second trihalomethane formation observed during the degradation of nevirapine and efavirenz through chlorination. Similarly, over a 10-hour period, distinct changes in $CHBr_2Cl$ formation were observed in both experiments. In the nevirapine degradation experiment, the average formation of $CHBr_2Cl$ was measured to be 25.83 µg/L. On the other hand, during the degradation of efavirenz, the average formation of $CHBr_2Cl$ was slightly lower, with a value of 23.36 µg/L. When comparing the $CHBr_2Cl$ formation between nevirapine and efavirenz degradation, it was found that nevirapine exhibited a 9.6% higher yield of $CHBr_2Cl$ compared to efavirenz. Nevirapine and efavirenz possess different molecular structures. The presence and arrangement of specific functional groups within their structures can influence their susceptibility to chlorination and bromination reactions (Westerhoff *et al.,* 2004). Probably, nevirapine's structure contains elements that are more prone to forming $CHBr_2Cl$ compared to efavirenz. Degradation by chlorination results displayed that a > 3 mg/l chlorine dosage effectively removed Nevirapine, achieving a removal rate of 97%. However, this specific chlorine dosage also yielded a $CHBr_2Cl$ formation of > 98%.

$CHBr_3$ was the third trihalomethane formation observed during the degradation of nevirapine and efavirenz through chlorination. Likewise, over a 10-hour period, distinct changes in $CHBr_3$ formation were observed in both experiments. In the nevirapine degradation experiment, the average formation of $CHBr_3$ was measured to be 11.94 µg/L. On the other hand, during the degradation of efavirenz, the average formation of $CHBr_3$ was below 1 µg/L. When comparing the $CHBr_3$ formation between nevirapine and efavirenz degradation, it was found that nevirapine exhibited a significantly higher yield of $CHBr_3$, with a 91.62% increase compared to efavirenz. Bromination reactions can be highly dependent on the presence of suitable reaction sites within a molecule (Chanda and Fokin, 2009). Hence, nevirapine may have been more favorable to bromination sites or had a higher susceptibility to bromination due to its structural features (Letsoalo *et al.*, 2022).

Degradation of Nevirapine by chlorination resulted in the significant formation of > 90% $CHBr_3$, posing potential human health risks. Despite its high removal rates, the 5mg/l chlorine dosage raises concerns due to substantial trihalomethane formation.

In this study, among the three THMs investigated, $CHCl_3$ showed the highest formation rate. A possible explanation for this phenomenon is that both ARVs contain tertiary alkaloids containing tertiary amine functional groups, as well as the interaction between $CHBr_2Cl$ and dichloromethane (CH_2Cl_2) in the tap water which introduces quaternary ammonium moiety into $CHCl_3$ and leads to an increase in $CHCl_3$ formation. (Jordan and Gibb 2017). Nonetheless, the average $CHCl_3$ formation obtained from the investigation was still below 20% and was within the Environmental Protection Agency's maximum contaminant level in drinking water guidelines (80 g/L) (Ivahnenko and Zogorski 2006). $CHCl_3$ levels have also been reported in drinking water in Greece, Ireland, the United Kingdom, and Florida, ranging from 4% to 66% (McCulloch 2003; Whitaker *et al.* 2003). During the degradation of Efavirenz and Nevirapine, the results also showed an average total trihalomethane (TTHM) concentration of 133.38 µg/L. A comparison between the two studies revealed a significant increase of > 90% in TTHM formation when using a higher chlorine concentration of > 3 mg/L compared to the 1.5 mg/L (TTHM, 11.69 µg/L) used by Dong *et al.* (2020). This suggests that higher chlorine concentrations can lead to a substantial increase in the formation of TTHMs during the degradation process.

5.3.2 Reaction kinetics between trihalomethane and chlorine

The first order k_{obs} and the apparent second-order rate constant (k_{app}) values for the three identified trihalomethanes were calculated using equation (E.q.10) and (E.q.11), respectively, from chapter 4. Figure 28 below displays the comparison of measured trihalomethane K_{app} values from degradation of ARVs by chlorination.

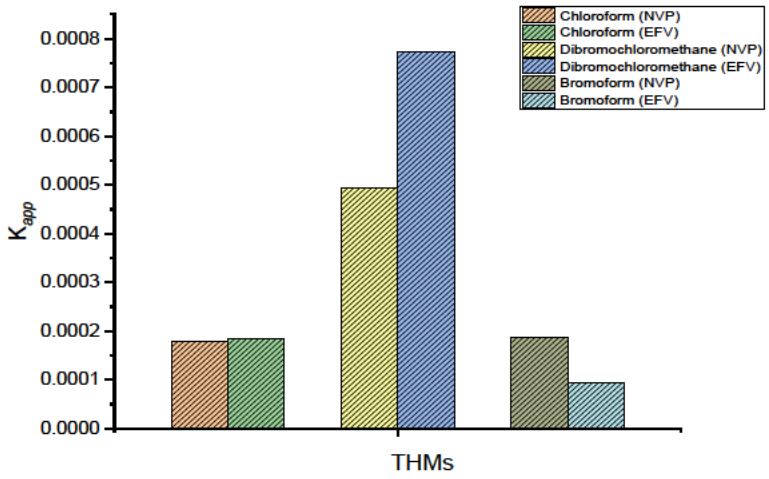


Figure 28: Comparison of Trihalomethane K_{app} values from Chlorination-Induced Degradation of Antiretroviral Drugs (ARVs)

The highest apparent second-order rate constant k_{app} value for the trihalomethanes was observed in $CHBr_2Cl$, with a value of 7.722 x 10^{-4} M^{-1}. s^{-1} , under the following conditions: 100 ug/L Efavirenz, 25°C, Cl_2- 0.1426 µM, pH 7.5. Conversely, the lowest K_{app} value for the trihalomethanes was observed in $CHBr_3$, with the K_{app} value of 9.33 x 10^{-4} M^{-1}. s^{-1} under the same conditions. The K_{app} rate constant value measured during the formation of $CHCl_3$ in the degradation of Efavirenz was approximately 2% higher than the K_{app} rate constant value measured during the degradation of Nevirapine. Similarly, the K_{app} rate constant value measured during the formation of $CHBr_2Cl$ in the degradation of Efavirenz was approximately 67% higher than the K_{app} rate constant value measured during the degradation of Nevirapine. However, the K_{app} rate constant value measured during the formation of bromoform in the degradation of Efavirenz was approximately 52% lower than the K_{app} rate constant value measured during the degradation of Nevirapine. Furthermore, the rate constant values determined during the degradation of Efavirenz by chlorination for $CHCl_3$ and $CHBr_2Cl$ formation were found to be higher than those observed during the degradation of Nevirapine. According to (Gallard and von Gunten, 2002), the formation of trihalomethane during the degradation of resorcinol yielded rate constants between 0.01 and 0.03 M^{-1}. s^{-1} under the following conditions of 50 µM > [Cl_2] > 210 µM, 25°C, and pH range 7–9 for surface waters. In this study, the formation of trihalomethane during the degradation of Nevirapine and Efavirenz in drinking water yielded K_{app} rate constant ranging between 9.33 x 10^{-4} and 7.722 x 10^{-4} M^{-1}. s^{-1} under the following conditions: 25°C, Cl_2 0.1426 µM, and pH 7.5.

Therefore, compared to both studies, the use of 210 µM Cl_2 yielded a 38-fold higher K_{app} rate constant compared to 0.1429 µM. The study revealed that the formation of $CHCl_3$ (63.49 g/L) during efavirenz degradation under specific conditions (25°C, 6 hours, pH 7.5, and 0.1429 µM residual chlorine) was the highest observed among the two ARVs. The K_{app} rate constants for $CHCl_3$ and $CHBr_2Cl$ formation during efavirenz degradation were higher compared to nevirapine degradation. However, the K_{app} rate constant for $CHBr_3$ during efavirenz degradation was approximately half of that observed during nevirapine degradation.

5.4 Conclusion

This study aimed to investigate the formation of trihalomethanes during the degradation of Nevirapine and Efavirenz through chlorination. It was found that under ideal conditions of pH 7.5, a temperature of 30°C, and a chlorine dosage exceeding 2 mg/L, the degradation of Nevirapine and Efavirenz reached 97% and 90%, respectively. To assess the formation of trihalomethanes, the optimal conditions identified were utilized. However, these conditions were found to be unfavorable for reducing THMs, as they resulted in an average increase of over 98% in THM formation. This finding raises concerns about the acceptability of using chlorine concentrations above 2 mg/L for disinfecting drinking water in an environmental setting. Hypothetically, a chlorine concentration of less than 1 mg/L may yield a THM formation below 50%. Among the trihalomethanes, the highest K_{app} value was observed in $CHBr_2Cl$, reaching 7.722×10^{-4} $M^{-1}. s^{-1}$ under similar pH and temperature conditions. Conversely, the lowest K_{app} value for the trihalomethanes was found in $CHBr_3$, with a K_{app} value of 9.33×10^{-4} $M^{-1}. s^{-1}$ under the same experimental conditions. It is important to note that the high formation of THMs could be detrimental to human health when consuming water. Therefore, caution should be exercised when considering the use of chlorine concentrations exceeding 2 mg/L in the disinfection of drinking water to minimize potential risks to human health.

Chapter 6: Major conclusion and recommendations

This study aimed to investigate the occurrence of selected ECs in DWTPs in KwaZulu-Natal and assess the impact of operational parameters on the removal of ECs during chlorination. The objectives of the study were to determine the levels of ECs in the source water and effluent of DWTPs. Secondly, to evaluate the removal efficiencies of selected ECs in different treatment units of DWTPs, Thirdly, to examine the influence of operational parameters such as initial chlorine concentration, pH, initial EC concentration, and temperature on EC removal during chlorination. Lastly, to analyse the formation of THMs during the degradation of ECs through chlorination.

6.1 Major Conclusions

The conclusions based on objectives of this study are:

- The results of a systematic review of EC pollution in aquatic sources revealed that South African research on ECs is falling behind when compared to other countries, highlighting the need for increased efforts nationally. There is a need for decentralized monitoring technologies in EC monitoring plans since poor sanitation, poor pit latrine management, and inadequate WWTPs contribute to EC discharge into surface water sources. In drinking water treatment plants, more effort is needed to increase EC monitoring due to the limited data available.
- The investigation of three drinking water treatment plants revealed the presence of all five ECs investigated in the present study. In the raw water effluent, the average concentrations of these ECs were as follows: sulfamethoxazole (114.37 ng/L), carbamazepine (118.69 ng/L), efavirenz (156.12 ng/L), nevirapine (164.06 ng/L), and atenolol (197.47 ng/L), respectively. The concentrations of the ECs in the treated effluent were as follows: Sulfamethoxazole (14.67 ng/L), Carbamazepine (23.80 ng/L), Efavirenz (21.80 ng/L), Nevirapine (24.08 ng/L), and Atenolol (45.44 ng/L), respectively.

Atenolol exhibited the highest concentration levels among all the ECs in both the raw water effluent and the treated effluent, while Sulfamethoxazole displayed the lowest concentration levels in both cases. At a pH of 3, the recoveries of various ECs using solid-phase extraction were as follows: Carbamazepine had a 71% recovery rate, Nevirapine and Efavirenz had an 80% recovery rate, Sulfamethoxazole had a 57% recovery rate, and Atenolol had a 30% recovery rate. These percentages represent the efficiency of the SPE method in extracting these specific ECs at that pH level.

- The removal rate at treatment steps varied; the various treatment units, including coagulation, sedimentation, sand filtering, and chlorination, exhibited different removal rates for the selected ECs, with chlorination showing the highest removal rate at 46.14% and coagulation displaying the lowest at 19.87%. Among the ECs studied, Nevirapine had the highest ROmax value (0.058) in the toddler category, suggesting that the level of Nevirapine occurrence in the drinking water supply of KZN should be continuously monitored and further measures are necessary to ensure their effective removal during the treatment process.

- Using laboratory-scale experiments, it was found that under ideal conditions (pH 7.5, a temperature of 30°C, chlorine dosage > 2 mg/L), the removal of nevirapine can be improved up to 97%, while efavirenz to 90%. The maximum K_{app} value achieved for Nevirapine was 109.67 x 10^{-2} M^{-1}. s^{-1} , obtained at an experimental pH of 7.5 and a temperature of 25°C. Similarly, for Efavirenz, the maximum K_{app} value recorded was 95.47 x 10^{-2} M^{-1}. s^{-1} under the same pH and temperature conditions. The minimum exposure times estimated for a 99% removal of 100 µg/L of Nevirapine and Efavirenz in a continuous stirred tank reactor were 284 mg min/L and 257 mg min/L, respectively. The Estimated HRT is 1.75 to 1.9 hours required for 99% removal of 100 µg/L of Nevirapine and Efavirenz at a chlorination dosage of 2mg/L, temperature 30^{o}C and pH 7.5.

The study can broadly assist in evaluating the application of chlorination for the removal of Nevirapine and Efavirenz from water and wastewater, as the process is cost-effective for developing countries such as South Africa, where large-scale implementation of sophisticated advanced oxidation processes is not economically affordable.

- Further investigations on THM formation during the above optimized conditions have shown the formation of THMs at a significant level, with $CHCl_3$ exhibiting the highest formation during the degradation of Efavirenz under specific conditions (pH 7.5, temperature 25°C, chlorine concentration 5 mg/L). On the other hand, $CHBr_2Cl$ displayed the highest K_{app} value of $7.722 \times 10^{-4}\ M^{-1}.\ s^{-1}$. This study also found a significant increase (>98%) in the formation of trihalomethanes (THMs) during the chlorination process of Nevirapine and Efavirenz under optimal conditions (pH 7.5, temperature 30°C, chlorine dosage > 2 mg/L), raising concerns about the acceptability of using chlorine concentrations > 2 mg/L for disinfecting drinking water.

6.2 Recommendation

- To get a comprehensive understanding of the EC pollution in South Africa, it is essential to expand the investigation beyond the five predominant ECs in drinking water and examine the occurrence and removal of a wide range of ECs. This will provide a better understanding of the sources of ECs and the effectiveness of different water treatment technologies for their removal. The findings could also inform the development of strategies to reduce the risk of ECs in drinking water.

- Exploring alternative disinfection methods such as ozonation, chloramination, and UV treatment in addition to chlorination in drinking water can provide insights into the degradation and formation behaviour of DBPs. Different kinetics, including the effects of pipe material, water distribution systems, and velocity, should be considered to evaluate the degradation, removal, and formation behaviour of DBPs.

Future research could also focus on other types and classes of disinfection by-products formation beyond trihalomethanes, including chlorite, halo acetic acids, bromate, nitrosamines, chloral hydrate, atrazine derived DBPs, and haloacetaldehydes.

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Appendix 1

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Review

Emerging contaminants in South African water environment- a critical review of their occurrence, sources and ecotoxicological risks

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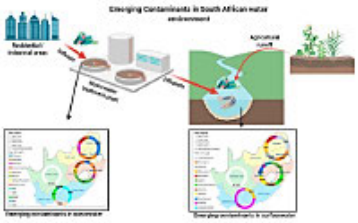
HIGHLIGHTS

- First report of quantitative analysis and mapping of EC pollution in South Africa.
- Concentration of DEP, DBP, BBP and DEHP is highest in untreated wastewater.
- Risk quotient of only 12 compounds out of 32 present in surface water, was <1.
- Urine diverted toilets and landfill leachate are identified as potential EC sources.

GRAPHICAL ABSTRACT



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ABSTRACT

The release of emerging contaminants (ECs) to the environment is a serious concern due to its health implications on humans, aquatic species, and the development of anti-microbial resistance. This review focuses on the critical analysis of available literature on the prevalence of ECs in the aquatic environment and their removal from wastewater treatment plants (WWTPs) in South Africa. Besides, a risk assessment is performed on the reported ECs from the South African surface water to augment the knowledge towards mitigation of EC pollution, and prioritisation of ECs to assist future monitoring plans and regulation framework. A zone wise classification approach was carried out to identify the spatial inferences and data deficiencies that revealed a non-uniformity in the monitoring of ECs throughout South Africa, with few zones rendering no data. The overarching data mining further revealed that unmanaged urine diverted toilets could be a potential source of EC pollution to groundwater in South Africa. Based on the available literature, it can be deduced that the complete adoption of EC management practices from developed countries might only contribute partly in the mitigation of EC pollution in South Africa. Therefore, an EC monitoring programme specific to the country is recommended which should be based on their occurrence levels, sources and removal in WWTPs.

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Appendix 2

Table 18: On-site sample testing results

DWTP1	Treatment units	pH	Temp °C	Salinity	µS/cm	Cl_2 (ppm)	TDS%	DO%
	Raw	6.8	21.17	0.06	122	0.05	0.079	71.6
	Sedimentation	7.17	21.34	0.05	103	0.04	0.067	52.6
	Sand filter	6.9	20.93	0.09	182	0.02	0.119	53.6
	Chlorination	7.09	21.17	0.09	191	0.17	0.125	58.4
DWTP2	**Treatment units**	**pH**	**Temp °C**	**Salinity**	**µS/cm**	**Cl_2 (ppm)**	**TDS%**	**DO%**
	Raw	7.23	23.09	0.07	148	0.06	0.096	48.83
	Sedimentation	8.03	22.94	0.07	159	0.03	0.103	52.6
	Sand filter	7.76	22.35	0.08	179	0.1	0.116	62.2
	Chlorination	7.26	22.46	0.07	158	0.16	0.010	48
DWTP3	**Treatment units**	**pH**	**Temp °C**	**Salinity**	**µS/cm**	**Cl_2 (ppm)**	**TDS%**	**DO%**
	Raw	7.53	23.11	0	9	0.07	0.006	31.2
	Coagulation	7.73	22.59	0	7	0.05	0.004	33.7
	Sedimentation	7.93	23.04	0.05	107	0.03	0.069	35.8
	Sand filter	7.88	22.9	0	7	0	0.004	38.9
	Chlorination	7.64	23.62	0.01	19	0.49	0.012	32.1

Table 19: Mass spectrometry optimized parameters

MS parameters	Values
Curtain Gas (CUR)	**35**
(Collision gas) CAD	**10**
IS (ion spray voltage)	**3500**
(Temperature (TEM)	**550**
(Nebulizing gas) GS1	**35**
(Nebulizing gas) GS2	**45**

Table 20: uHPLC gradient elution optimized parameters

LC PARAMETERS				
Time (min)	**Flow ml/min**	**A. conc %**	**B. conc %**	**Column °C**
	0.25	35	65	30
1	0.25	35	65	
2	0.25	35	95	
4	0.25	5	95	
7	0.25	5	95	
9	0.25	35	65	

Table 21: Trihalomethane working standards.

Calibration curve	**Chloroform**	**Dibromochloromethane**	**Bromoform**
Level 1	1,00	1,00	1,00
Level 2	2,50	2,50	2,50
Level 3	5,00	5,00	5,00
Level 4	10,00	10,00	10,00
Level 5	25,00	25,00	25,00
Level 6	50,00	50,00	50,00
Level 7	100,00	100,00	100,00

Table 22: Trihalomethane's Limit of Detection Values

Chloroform	**Dibromochloromethane**	**Bromoform**
0,10	0,01	0,01
0,10	0,01	0,01
0,10	0,01	0,01
0,10	0,01	0,01
0,10	0,01	0,01
0,10	0,01	0,01
0,10	0,01	0,01

Table 23: Trihalomethane's Limit of Quantification Values

Chloroform	**Dibromochloromethane**	**Bromoform**
0,50	0,10	0,10
0,50	0,10	0,10
0,50	0,10	0,10
0,50	0,10	0,10
0,50	0,10	0,10
0,50	0,10	0,10
0,50	0,10	0,10

Table 24: Antiretroviral Drug Degradation and Trihalomethane Formation: Experimental Procedure with Chlorination

Trihalomethane Experiment	EFV control	Water sample	EFV optimum conditions	NVP control	NVP optimum conditions
Temp °C	25	25	25	25	25
Cl_2 (ppm)	0	0	5	0	5
pH	7.5	7.5	7.5	7.5	7.5
Concentration (µg/L)	100	0	100	100	100

Initial concentration experiment	EFV control	EFV/NVP (1)	EFV/NVP (2)	EFV/NVP (3)	EFV/NVP (4)	EFV/NVP (5)
Temp °C	25	25	25	25	25	25
Cl_2 (ppm)	1	1	1	1	1	1
pH	7.5	7.5	7.5	7.5	7.5	7.5
Concentration (µg/L)	100	25	50	100	150	200

Chlorine Experiment	EFV control	EFV/NVP (1)	EFV/NVP (2)	EFV/NVP (3)	EFV/NVP (4)	EFV/NVP (5)
Temp °C	25	25	25	25	25	25
Cl_2 (ppm)	0.2	0.5	1	2	3	5
pH	7.5	5.5	6.5	7	7.5	8
Concentration (µg/L)	100	100	100	100	100	100

pH experiment	EFV control	EFV/NVP (1)	EFV/NVP (2)	EFV/NVP (3)	EFV/NVP (4)	EFV/NVP (5)
Temp °C	25	25	25	25	25	25
Cl_2 (ppm)	1	1	1	1	1	1
pH	7.5	5.5	6.5	7	7.5	8
Concentration (µg/L)	100	100	100	100	100	100

Temperature experiment	EFV control	EFV/NVP (1)	EFV/NVP (2)	EFV/NVP (3)	EFV/NVP (4)	EFV/NVP (5)
Temp °C	25	10	15	20	25	30
Cl_2 (ppm)	1	1	1	1	1	1
pH	7.5	7.5	7.5	7.5	7.5	7.5
Concentration (µg/L)	100	100	100	100	100	100

Table 25: Comparison of Antiretroviral (ARVs) drugs in South Africa to global average in freshwater

ARVs	Water type	Con. (ng/L)	Region/Country	Reference
Abacavir	Surface water	<LOQ(0.04)	SA	(Wood et al., 2015)
		1.4	Hessian Ried, Germany	(Prasse et al., 2010)
		2.6 ± 1.7	France	(Aminot *et al.* 2016)
	Ground water	<LOQ (0.02)	North West and Gauteng Provinces, SA	(Swanepoel *et al*. 2015)
		11	Koblenz, Germany	(Boulard *et al.* 2018)
	Drinking water	0.5	Municipal tap water, SA	(Swanepoel *et al.* 2015)
		n/a	Volvic water (PET bottles)/France	(Dévier *et al*. 2013)
Efavirenz	Surface water	354	Juskei River, SA	(Rimayi *et al.* (2018)
	Ground water	71	Gauteng Province, SA	(Rimayi *et al*. 2018)
	Drinking water	<LOQ (0.1)	Municipal tap water, SA	Swanepoel *et al*. (2015)
Emtricitabine	Surface water	13	Juskei River, SA	(Rimayi *et al*. 2018)
Lamivudine	Surface water	242	SA	(Wood *et al.* 2015)
		4 to 9	Yodo River basin, Japan	(Azuma *et al.* 2015)
		20	River Rhine, Koblenz, Germany	(Boulard *et al*. 2018)
		12	Lake Päijänne, Finland	(Ngumba *et al.* 2016)
		4.1 ± 2.5	France	(Aminot *et al.* 2015)
		167,100	Kisumu, Kenya	(K'oreje *et al.* 2016)
	Ground water	<LOQ (1)	North West and Gauteng Provinces, SA	(Swanepoel *et al*. 2015)
		25.2	USA	(Fisher *et al*. 2016)
		1.8	Koblenz, Germany	(Boulard *et al.* 2018)
	Drinking water	4	Drinking water treatment plants/USA	(Furlong *et al.* 2017)
		<1	Treated drinking water/Germany	(Boulard *et al.* 2018)
Nevirapine	Surface water	1,480	South Africa	(Wood *et al*. 2015)
		5,620	Kisumu, Kenya	(K'oreje *et al.* 2016)
		1.3 ± 0.6	France	(Aminot *et al*. 2015)
		n.d.	Lake Päijänne, Finland	(Ngumba *et al*. 2016)
	Ground water	13	Hartbeespoort Dam catchment, SA	(Rimayi *et al*. 2018)
		27.73	USA	(Fisher *et al*. 2016)
		1600	Kisumu, Kenya	(K'oreje *et al*. 2016)
	Drinking water	<LOQ (92.7)	Tap water/Hartbeespoort Dam, SA	(Wood *et al.* 2015)

Zidovudine	Surface water	973	South Africa	(Wood *et al*. 2015)
		17410	Kisumu, Kenya	(K'oreje *et al.* 2012)
		170	Hessian Ried, Germany	(Prasse *et al.* 2010)
		33	France	(Aminot *et al*. 2015)
	Ground water	<LOQ(0.3)	North West and Gauteng Provinces, SA	(Swanepoel *et al*. 2015)
		30	Kisumu, Kenya	(K'oreje *et al.* 2016)
	Drinking water	72.7	Tap water/Hartbeespoort Dam, SA	(Wood *et al.* 2015)

Table 26: Comparison of Antiretroviral (ARVs) drugs in South Africa to global average in wastewater

ARVs	**Sewage water**		**Region/Country**	**Reference**
	Influent	**Effluent**		
Abacavir	225 ± 40	<LOQ (0.5)	Germany	(Prasse *et al*. 2010)
	3500 ± 210	<LOQ (0.5)	Northern KwaZulu-Natal, SA	(Abafe *et al*. 2018)
	14,000 ± 2300	<LOQ (0.5)	Phoenix KwaZulu-Natal, SA	(Abafe *et al*. 2018)
Efavirenz	34,000 ± 2400	20,000 ± 2000	Phoenix KwaZulu-Natal, SA	(Abafe *et al*. 2018)
	5,500	14,000	Gauteng, SA	(Schoeman *et al.* 2015)
	12,090	4,040	Kakamega, Gauteng, SA	(Schoeman *et al*. 2017)
	1,020	110	Kisat, Kisumu, Kenya	(K'oreje *et al.* 2016))
	15.4	9.15	Western Cape, SA	(Mosekiemang *et al*. 2019)
Emtricitabine	172	41.7	Western Cape, SA	Mosekiemang et al.(2019)
	980± 50	<LOQ (20)	Germany	(Funke *et al.* 2016)
Lamivudine	720±130	<LOQ (100)	Germany	(Prasse *et al*. 2010)
	20.9	<LOQ (661)	Western Cape, SA	(Mosekiemang *et al*.2019)
	2,200 ± 190	<LOQ (20)	KwaZulu-Natal, SA	(Abafe *et al.* 2018)
	60,680	31070	Nyalenda, Kisumu, Kenya	(K'oreje *et al*. 2016)
	55	n/a	France	(Aminot *et al*. 2015)
	507 ± 80	n.d.	Lede, Belgium	(Vergeynst *et al.* 2015)
Nevirapine	2,800 ± 190	1,400 ± 63	Phoenix KwaZulu-Natal, SA	(Abafe *et al.* 2018)
	53	92	Kitale, Gauteng, SA	(Schoeman *et al*. 2017)
	3,300	2,110	Nyalenda, Kisumu, Kenya	(K'oreje *et al.* 2016)
	21.8 ± 2.3	32.1 ± 0.5	Germany	(Prasse *et al*. 2010)
	19	n/a	yväskylä, Finland	(Ngumba *et al*. 2016)
Zidovudine	n.d	n.d	Western Cape, SA	(Mosekiemang *et al.* 2019)

	53,000 ± 3600	500 ± 86	KwaZulu-Natal, SA	(Abafe *et al.* 2018)
	62	37	Jyväskylä, Finland	(Ngumba *et al*. 2016)
	<LOQ	<LOQ	Guangzhou, China	(Peng *et al.* 2014)
	390 ± 33	150 ± 27	Germany	(Funke *et al*. 2016)
	20,130	n/a	Kisat, Kisumu, Kenya	(K'oreje *et al.* 2016)

Table 27: Toxicological data (mg/L) for algae, crustaceans and fish and calculated PNECs (ng/L) for detected emerging compounds present in surface water across South Africa.

Name of Compound	Algae	Crustaceans	Fish	Assessment Factor	Selected Data	PNEC (mg/L)	PNEC (ng/L)	Compound category	Reference for toxicological data.
Acetaminophen	0.005	0.32	500	10	0.005	0.0005	500	NSAIDs	(Dave and Herger, 2012; Henschel *et al.*, 1997; Kim *et a*l., 2011)
Ampicillin						0.000075	75	antibiotic	(de Souza *et al*.2009)
Aspirin	3.282	1.24	22.8	1000	1.24	0.00124	1240	NSAID	(Zhoua *et. al* 2019)
Atenolol	10	9.45*	5	50	5	0.1	100000	NSAID	(Fraysse and Garric, 2005; Winter *et al*., 2008; Yamamoto *et al.*, 2007)
Atrazine						0.000044	44	Herbicides	(Zheng *et al.* 2017)
Azithromycin	1.847	3.023	21.945	1000	1.847	0.001847	1847	Antibiotics	((Zhoua *et. al* 2019)
Bezafibrate	60	0.023	5.3	100	0.023	0.00023	230	NSAID	(Isidori *et al*., 2007; Sanderson *et al*., 2003)
Caffeine	0.005	0.005	0.032	10	0.0032	0.00032	320	Human indicators	(Zhoua *et. al* 2019)
Carbamazepine	0.5	0.0001	0.1	10	0.0001	0.00001	10	Antiretroviral	(Zhoua *et. al* 2019)
Chloramphenicol	2.5	2	38.821	50	2	0.04	40000	antibiotic	(Zhoua *et. al* 2019)
Ciprofloxacin	0.005	60	100	50	0.005	0.0001	100	antibiotic	(Zhoua *et. al* 2019)
Clarithromycin	0.002	8.16	1000	100	0.002	0.00002	20	Antibiotics	(Zhoua *et. al* 2019)
Diclofenac	0.005	0.00001	0.0015	10	0.00001	0.000001	1	NSAIDs	(Zhoua *et. al* 2019)

Efavirenz	0.686	0.141	0.13	1000	0.13	0.00013	130	Antiretroviral	(Musee and Makhaye 2019)
Erythromycin	0.002	25	100	10	0.002	0.0002	200	antibiotic	(Zhoua *et. al* 2019)
Fluoxetine	0.072	0.01	0.00003	10	0.00003	0.000003	3	Anti-depressants	(Zhoua *et. al* 2019)
Ibuprofen	2	20	0.0001	10	0.0001	0.00001	10	NSAIDs	(Han *et al.,* 2006: Han *et al*., 2010: Yamamoto *et al.,* 2007)
Ketoprofen	3.282	1.24	22.8	1000	1.24	0.00124	1240	NSAIDs	(Harada *et al.,* 2008: Sanderson *et al.,* 2003)
Lamivudine	1790	162	14300	1000	162	0.162	162000	Antiretroviral	(Musee and Makhaye 2019)
Metformin	320	64	982	1000	64	0.064	64000	Diabetes	(Van der Aa *et al*.2011)
nalidixic acid	1800	3290	4420	1000	1800	1.8	1800000	antibiotic	(Zhoua *et. al* 2019)
Nevirapine	0.167	1.621	3.523	1000	0.167	0.000167	167	Antiretroviral	(Zhoua *et. al* 2019)
Stavudine	0.017	4742.621	19.295	1000	0.017	0.000017	17	Antiretroviral	(Zhoua *et. al* 2019)
Streptomycin						0.00016	160	antibiotic	(Tell *et.al* 2019)
Sulfamethoxazole	1	1.563	>104	50	1	0.02	20000	antibiotic	(De Liguoro *et al.,* 2009: Kim *et al.,* 2007: Yang *et al.,* 2008
Sulfasalazine	75.394	19.551	39.84	100	19.551	0.19551	195510	Antibiotics	(Zhoua *et. al* 2019)
Tenofovir						0.000248	248	Antiretroviral	N. Musee and N.Makhaye (2019)
tetracycline	0.05	0.01	0.0005	10	0.01	0.001	1000	antibiotic	(Zhoua *et. al* 2019)
Trimethoprim	16	3.12	25	10	3.12	0.312	312000	Antibiotics	(De Liguoro *et al.,* 2012: Yang *et al*., 2008)
Tylosin	0.064	79.099	164.658	100	79.099	0.79099	790990	antibiotic	(Zhoua *et. al* 2019)
Zalcitabine						0.00472	4720	Antiretroviral	(N. Musee and N.Makhaye 2019)
Zidovudine	0.02	539.7	318.28	10	0.02	0.002	2000	Antiretroviral	(Zhoua *et. al* 2019)

The table provided above represents the publication output of my PhD research work, as extracted from the following source: Gani, K. M., Hlongwa, N., Abunama, T., Kumari, S. and Bux, F. 2021. "Emerging contaminants in the South African water environment: A critical review of their occurrence, sources, and eco-toxicological risks." Published in Chemosphere, Volume 269, and page 128737.

Table 28: Removal of various ECs in different wastewater treatment plants of South Africa. (Abbreviations, PST: primary settling tank; SST: Secondary settling tank; AST: Activated sludge Tank. UV: Ultraviolet; BNR:Biological nutrient removal)

North Zone						
Name of Compound	**WWTP technology**	**WWTP capacity (MLD)**	**Influent conc (ng/L)**	**Effluent conc (ng/L)**	**% Removal efficiency**	**Reference**
ibuprofen	PST+5-stage phoredox process (ASP)+SST+Chlorination	150	39800	12600	68.3	(Amdany *et al*., 2014)
Naproxen	PST+5-stage phoredox process (ASP)+SST+Chlorination	150	55000	13500	75.5	(Amdany *et al*., 2014)
Triclosan	PST+5-stage phoredox process (ASP)+SST+Chlorination	150	78400	10700	86.4	(Amdany *et al*., 2014)
Ribavirin	PST+Anaerobic+NitrifyingTrickling filter + Anoxic +Aerobic +SST+Chlorination		20	0.04	99.8	(Osunmakinde *et al.,* 2013)
Famciclovir (Famvir)	PST+Anaerobic+NitrifyingTrickling filter + Anoxic +Aerobic +SST+Chlorination		21	0.06	99.7	Osunmakinde *et al.*, 2013)
Efavirenz	PST+Anoxic tank+Aeration tank+SST+Chlorination		13000	12000	7.7	(Schoeman *et al*., 2017)
Nevirapine	PST+Anoxic tank+Aeration tank+SST+Chlorination		490	190	61.2	(Schoeman *et al*., 2017)
Ciprofloxacin	Aeration tank+SST+ Maturation pond+Chlorination	0.322	990	510	48.5	(Kanama *et al*.2018)
norfloxacin	Aeration tank+SST+ Maturation pond+Chlorination	0.322	420	120	71.4	(Kanama *et al*.2018)
tetracycline	Aeration tank+SST+ Maturation pond+Chlorination	0.322	11040	950	91.4	(Kanama *et al*.2018)
Atenolol	Aeration tank+SST+ Maturation pond+Chlorination	0.322	4410	1190	73.0	(Kanama *et al*.2018)

triclocarban	Aeration tank+SST+ Maturation pond+Chlorination	0.322	760	110	85.5	(Kanama *et al*.2018)
Diclofenac	Aeration tank+SST+ Maturation pond+Chlorination	0.322	2360	300	87.3	(Kanama *et al*.2018)
Acetaminophen	Aeration tank+SST+ Maturation pond+Chlorination	0.322	49790	6100	87.7	(Kanama *et al*.2018)
Ibuprofen	Aeration tank+SST+ Maturation pond+Chlorination	0.322	16440	5230	68.2	(Kanama *et al*.2018)
Ketoprofen	Aeration tank+SST+ Maturation pond+Chlorination	0.322	390	140	64.1	(Kanama *et al*.2018)
Estrone	Aeration tank+SST+ Maturation pond+Chlorination	0.322	31	23	25.8	(Kanama *et al*.2018)
Estriol	Aeration tank+SST+ Maturation pond+Chlorination	0.322	463	23	95.0	(Kanama *et al*.2018)
17 *b*-estradiol	Aeration tank+SST+ Maturation pond+Chlorination	0.322	22	14	36.4	(Kanama *et al*.2018)
17α-ethinylestradiol	Aeration tank+SST+ Maturation pond+Chlorination	0.322	5601	1344	76.0	(Kanama *et al*.2018)
Triclosan	PST+AST+SST+Chlorination	20	17600	2010	88.6	(Lehutso *et al*.2017)
Triclosan	PST+biofilter+AST+SST+ chlorination+UV	50	13000	990	92.4	(Lehutso *et al*.2017)
Triclocarban	PST+biofilter+AST+SST+ chlorination+UV	50	2840	86	97.0	(Lehutso *et al*.2017)
brominated diphenyl ethers(17)	N/A	N/A	0.026	0.014	46.2	(Sibiya, *et al*.2017)
brominated diphenyl ethers(17)	N/A	N/A	0.036	0.006	83.3	(Sibiya, *et al*.2017)
brominated diphenyl ethers(17)	N/A	N/A	0.028	0.026	7.1	(Sibiya, *et al*.2017)
brominated diphenyl ethers(17)	N/A	N/A	0.03	0.024	20.0	(Sibiya, *et al*.2017)
brominated diphenyl ethers(17)	N/A	N/A	0.009	0.006	33.3	(Sibiya, *et al*.2017)

brominated diphenyl ethers(17)	N/A	N/A	0.07	0.042	40.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(28)	N/A	N/A	0.024	0.012	50.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(28)	N/A	N/A	0.048	0.036	25.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(28)	N/A	N/A	0.026	0.026	0.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(28)	N/A	N/A	0.048	0.039	18.8	(Sibiya, *et al.*2017)
brominated diphenyl ethers(28)	N/A	N/A	0.039	0.01	74.4	(Sibiya, *et al.*2017)
brominated diphenyl ethers(28)	N/A	N/A	0.06	0.036	40.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.094	0.094	0.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.047	0.0094	80.0	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.176	0.05	71.6	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.092	0.083	9.8	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.192	0.138	28.1	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.141	0.035	75.2	(Sibiya, *et al.*2017)
brominated diphenyl ethers(47)	N/A	N/A	0.235	0.141	40.0	(Sibiya, *et al.*2017)
Nevirapine	Activated sludge+MBR+chlorination	55	10	10	0.0	(Mosekiemang *et al.*2019)
Lamivudine	Activated sludge+MBR+chlorination	55	48.7	3.67	92.5	(Mosekiemang *et al.*2019)
emtricitabine	Activated sludge+MBR+chlorination	55	352	0.721	99.8	(Mosekiemang *et al.*2019)
12-hydroxy-Nevirapine	Activated sludge+MBR+chlorination	55	4.3	0.519	87.9	(Mosekiemang *et al.*2019)
Nevirapine	Activated sludge+MBR+UV	46	1.43	0.658	54.0	(Mosekiemang *et al.*2019)

Efavirenz	Activated sludge+MBR+chlorination	55	8.2	0.982	88.0	(Mosekiemang *et al*.2019)
8,14-dihydroxy- Efavirenz	Activated sludge+MBR+chlorination	55	15.2	1.48	90.3	(Mosekiemang *et al*.2019)
Desthiazo-lylmethyloxycarbonyl Ritonavir	Activated sludge+MBR+chlorination	55	20	0.787	96.1	(Mosekiemang *et al*.2019)
Emtricitabine	Activated sludge+MBR+chlorination	55	350	110	68.6	(Mosekiemang *et al*.2019)
12-hydroxy Nevirapine	Activated sludge+MBR+chlorination	55	10	10	0.0	(Mosekiemang *et al*.2019)
Efavirenz	Activated sludge+MBR+UV	46	15	5	66.7	(Mosekiemang *et al*.2019)
8,14-dihydroxy Efavirenz	Activated sludge+MBR+UV	46	13	10	23.1	(Mosekiemang *et al*.2019)
Ritonavir	Activated sludge+MBR+UV	46	15	10	33.3	(Mosekiemang *et al*.2019)
Emtricitabine	Activated sludge+MBR+UV	46	15	5	66.7	(Mosekiemang *et al*.2019)
cocaine	UCT (BNR)+ MLE+SST	55	147	27.6	81.2	(Archeret *et.al.*(2017)
methamphetamine	UCT (BNR)+ MLE+SST	55	450.2	270.9	39.8	(Archeret *et.al.*(2017)
mephedrone	UCT (BNR)+ MLE+SST	55	120.6	35.6	70.5	(Archeret *et.al.*(2017)
South Zone						
Name of Compound	**WWTP technology**	**WWTP capacity (PE)**	**Influent conc (ng/L)**	**Effluent conc (ng/L)**	**% Removal efficiency**	**Reference**
diethyl phthalates	PST+AS (BNR)+SST+Chlorination+AD+Dew	900000 PE	1506000	272000	81.9	(Olujimi *et al*.2012)
2-nitrophenol	PST+AS (BNR)+SST+Chlorination+AD+Dew	900000 PE	115000	79000	31.3	(Olujimi *et al*.2012)
dibutyl phthalate;	PST+AS (BNR)+SST+Chlorination+AD+Dew	900000 PE	140000	83000	40.7	(Olujimi *et al*.2012)
diethylhexyl phthalate	PST+AS (BNR)+SST+Chlorination+AD+Dew	900000 PE	60000	20000	66.7	(Olujimi *et al*.2012)
phenol	PST+AS (BNR)+SST+Chlorination+AD+Dew	900000 PE	823000	150000	81.8	(Olujimi *et al*.2012)
dibutyl phthalate	PST+AS (BNR)+SST+Chlorination+AD+Dew	900000 PE	5267000	1049000	80.1	(Olujimi *et al*.2012)
diethyl phthalates	PST+AS (BNR)+SST+Chlorination	900000 PE	3917000	123000	96.9	(Olujimi *et al*.2012)
East zone						

Name of Compound	WWTP technology	WWTP capacity (MLD)	Influent conc (ng/L)	Effluent conc (ng/L)	% Removal efficiency	Reference
ibuprofen	PST+AS+SST+Chlorination	75	1200	1100	8.3	(Matongo *et al.*, 2015)
Ketoprofen			6400	4300	32.8	(Madikizela *et al*., 2014)
Erythromycin	PST+AS+SST+Chlorination	75	600	200	66.7	(Matongo *et al.*, 2014)
Triclosan	PST+AS+SST+Chlorination	75	9000	6400	28.9	(Matongo *et al.*, 2015)
Carbamazepine	AS+SST+Chlorination		2200	900	59.1	(Madikizela *et al.*, 2014)
Clozapine	PST+AS+SST+Chlorination	75	9600	8600	10.4	(Matongo *et al.*, 2015)
Caffeine	PST+AS+SST+Chlorination	75	4500	600	86.7	(Matongo *et al.*, 2015)
Oestrone (E1)	PST+AS+SST+Chlorination	75	62	23	62.9	(Manickum and John, (2014)
Oestradiol (E2)	PST+AS+SST+Chlorination	75	112	28	75.0	(Manickum and John, 2014)
Ethynyl-oestradiol (EE3)	PST+AS+SST+Chlorination	75	18	3	83.3	(Manickum and John, 2014)
Progesterone (P)	PST+AS+SST+Chlorination	75	393	2	99.5	(Manickum and John, 2014)
Testosterone (T)	PST+AS+SST+Chlorination	75	832	13	98.4	(Manickum and John, 2014)
ibuprofen	N/A	N/A	69000	2100	97.0	(Madikizela and Chimuka2017)
Naproxen	N/A	N/A	20000	600	97.0	(Madikizela and Chimuka2017)
Diclofenac	N/A	N/A	16000	1400	91.3	(Madikizela and Chimuka2017)
ibuprofen	N/A	N/A	55000	4200	92.4	(Madikizela and Chimuka2017)
Naproxen	N/A	N/A	15000	1100	92.7	(Madikizela and Chimuka2017)
Diclofenac	N/A	N/A	6400	2000	68.8	(Madikizela and Chimuka2017)
tetracycline	BNR+SST+Maturation ponds+Chlorination	53	5680	640	88.7	(Agunbiade and moodley,2014)
Abacavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	<LOD	<LOD		(Abafe *et al*.2018)

Maraviroc	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	83	<LOD		(Abafe *et al*.2018)
Zidovudine	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	53000	500	99.1	(Abafe *et al*.2018)
Nevirapine	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	2100	1900	9.5	(Abafe *et al*.2018)
Raltegravir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	17000	3500	79.4	(Abafe *et al*.2018)
Darunavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	43000	17000	60.5	(Abafe *et al*.2018)
Saquinavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	<LOD	<LOD		(Abafe *et al*.2018)
Atazanavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	64	78	-21.9	(Abafe *et al*.2018)
Indinavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	260	25	90.4	(Abafe *et al*.2018)
Ritonavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	3200	1500	53.1	(Abafe *et al*.2018)
Lopinavir	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	2500	3800	-52.0	(Abafe *et al*.2018)
Lamivudine	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	2200	130	94.1	(Abafe *et al*.2018)

Efavirenz	settling chamber+ anaerobic baffled reactor (ABR)+ anaerobic filter +constructed wetlands	0.04	34000	34000	0.0	(Abafe *et al.*2018)
Abacavir	BNR+SST+Maturation ponds+Chlorination	53	3500	<LOD		(Abafe *et al.*2018)
Maraviroc	BNR+SST+Maturation ponds+Chlorination	53	32	<LOD		(Abafe *et al.*2018)
Zidovudine	BNR+SST+Maturation ponds+Chlorination	53	6900	87	98.7	(Abafe *et al.*2018)
Nevirapine	BNR+SST+Maturation ponds+Chlorination	53	670	540	19.4	(Abafe *et al.*2018)
Raltegravir	BNR+SST+Maturation ponds+Chlorination	53	810	86	89.4	(Abafe *et al.*2018)
Darunavir	BNR+SST+Maturation ponds+Chlorination	53	920	350	62.0	(Abafe *et al.*2018)
Saquinavir	BNR+SST+Maturation ponds+Chlorination	53	<LOD	<LOD		(Abafe *et al.*2018)
Atazanavir	BNR+SST+Maturation ponds+Chlorination	53	1400	740	47.1	(Abafe *et al.*2018)
Indinavir	BNR+SST+Maturation ponds+Chlorination	53	590	42	92.9	(Abafe *et al.*2018)
Ritonavir	BNR+SST+Maturation ponds+Chlorination	53	1600	910	43.1	(Abafe *et al.*2018)
Lopinavir	BNR+SST+Maturation ponds+Chlorination	53	1300	3800	-192.3	(Abafe *et al.*2018)
Lamivudine	BNR+SST+Maturation ponds+Chlorination	53	840	<LOD		(Abafe *et al.*2018)
Efavirenz	BNR+SST+Maturation ponds+Chlorination	53	24000	33000	-37.5	(Abafe *et al.*2018)
Abacavir	BNR+SST+Maturation ponds+Chlorination	18	14000	<LOD		(Abafe *et al.*2018)
Maraviroc	BNR+SST+Maturation ponds+Chlorination	18	82	39	52.4	(Abafe *et al.*2018)

Zidovudine	BNR+SST+Maturation ponds+Chlorination	18	11000	430	96.1	(Abafe *et al.*2018)
Nevirapine	BNR+SST+Maturation ponds+Chlorination	18	2800	1400	50.0	(Abafe *et al.*2018)
Raltegravir	BNR+SST+Maturation ponds+Chlorination	18	61	<LOD		(Abafe *et al.*2018)
Darunavir	BNR+SST+Maturation ponds+Chlorination	18	69	130	-88.4	(Abafe *et al.*2018)
Saquinavir	BNR+SST+Maturation ponds+Chlorination	18	180	<LOD		(Abafe *et al.*2018)
Atazanavir	BNR+SST+Maturation ponds+Chlorination	18	210	300	-42.9	(Abafe *et al.*2018)
Indinavir	BNR+SST+Maturation ponds+Chlorination	18	300	40	86.7	(Abafe *et al.*2018)
Ritonavir	BNR+SST+Maturation ponds+Chlorination	18	1600	460	71.3	(Abafe *et al.*2018)
Lopinavir	BNR+SST+Maturation ponds+Chlorination	18	1200	1900	-58.3	(Abafe *et al.*2018)
Lamivudine	BNR+SST+Maturation ponds+Chlorination	18	1900	<LOD		(Abafe *et al.*2018)
Efavirenz	BNR+SST+Maturation ponds+Chlorination	18	34000	20000	41.2	(Abafe *et al.*2018)

The table provided above represents the publication output of my PhD research work, as extracted from the following source: Gani, K. M., Hlongwa, N., Abunama, T., Kumari, S. and Bux, F. 2021. "Emerging contaminants in the South African water environment: A critical review of their occurrence, sources, and eco-toxicological risks." Published in Chemosphere, Volume 269, and page 128737.

Table 29: Occurrence of ECs in urine diverted toilets in South Africa.

Name of Compound	(ng/L)	Compound category	Location	Reference
Atazanavir	2500	Antiviral	eThekwini nearby households	(Bischel *et al*. 2015)
Atenolol	31000	Beta-blocker	eThekwini nearby households	(Bischel *et al*. 2015)
Atenolol acid	98000	human metabolite	eThekwini nearby households	(Bischel *et al*. 2015)
Clarithromycin	17000	Macrolide antibacterial	eThekwini nearby households	(Bischel *et al*. 2015)
Darunavir	<1000	Antiviral	eThekwini nearby households	(Bischel *et al*. 2015)
Diclofenac	30000	Analgesic	eThekwini nearby households	(Bischel *et al*. 2015)
Emtricitabine	101000	Antiviral	eThekwini nearby households	(Bischel *et al*. 2015)
Hydrochlorothiazide	42000	Diuretic	eThekwini nearby households	(Bischel *et al*. 2015)
N4 Acetyl- sulfamethoxazole	360000	human metabolite	eThekwini nearby households	(Bischel *et al*. 2015)
Ritonavir	1600	Antiviral	eThekwini nearby households	(Bischel *et al*. 2015)
Sulfamethoxazole	2300000	Sulfonamide antibacterial	eThekwini nearby households	(Bischel *et al*. 2015)
Trimethoprim	19000	Antibacterial	eThekwini nearby households	(Bischel *et al*. 2015)

Table 30: Occurrence of emerging contaminants in the landfill leachates present in different regions of South Africa.

Name of Compound	(ng/L)	Compound category	Location	Reference
PCB-28	280	polybrominated diphenyl ethers	Mariannhill Landfill, near Durban	(Nomngongo *et al*.2012)
PCB-101	310	polybrominated diphenyl ethers	Mariannhill Landfill, near Durban	(Nomngongo *et al*.2012)
PentaBDE	407.29	congeners of PBDE	Bellville, landfill, Cape town	(Daso *et.al* (2013)
PentaBDE	985.22	congeners of PBDE	Coastal Park, landfill, Cape town	(Daso *et.al* (2013)
PentaBDE	1466.47	congeners of PBDE	Visserhok, landfill, Cape town	(Daso *et.al* (2013)
OctaBDE	14.33	congeners of PBDE	Bellville, landfill, Cape town	(Daso *et.al* (2013)
OctaBDE	6.18	congeners of PBDE	Coastal Park, landfill, Cape town	(Daso *et.al* (2013)
OctaBDE	15.87	congeners of PBDE	Visserhok, landfill, Cape town	(Daso *et.al* (2013)
decaBDE	398.11	congeners of PBDE	Bellville, landfill, Cape town	(Daso *et.al* (2013)
decaBDE	58.94	congeners of PBDE	Coastal Park, landfill, Cape town	(Daso *et.al* (2013)
decaBDE	1072.53	congeners of PBDE	Visserhok, landfill, Cape town	(Daso *et.al* (2013)
BDE (28)	52.4	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)

BDE (47)	924	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)
BDE (100)	17	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)
BDE (99)	68	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)
BDE (154)	13.7	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)
BB (153)	16.2	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)
BDE (183)	32.9	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)
BDE (209)	9770	PBDE congeners	Zandvliet WWTP, Cape town	(Daso *et.al* (2013)

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Appendix 3

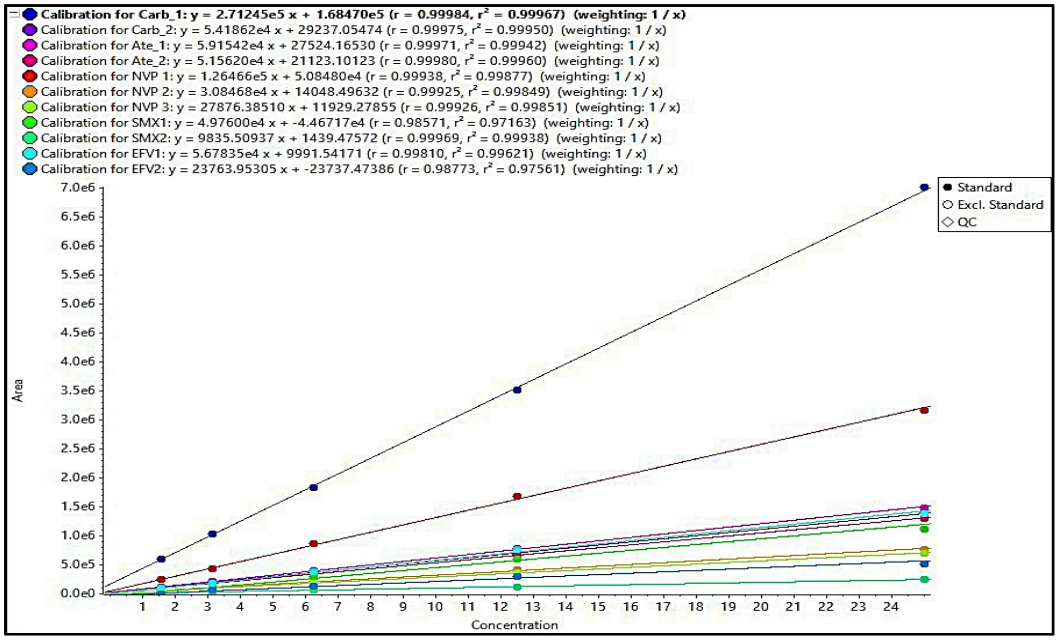

Figure 29: Calibration Curves for selected Emerging Contaminants

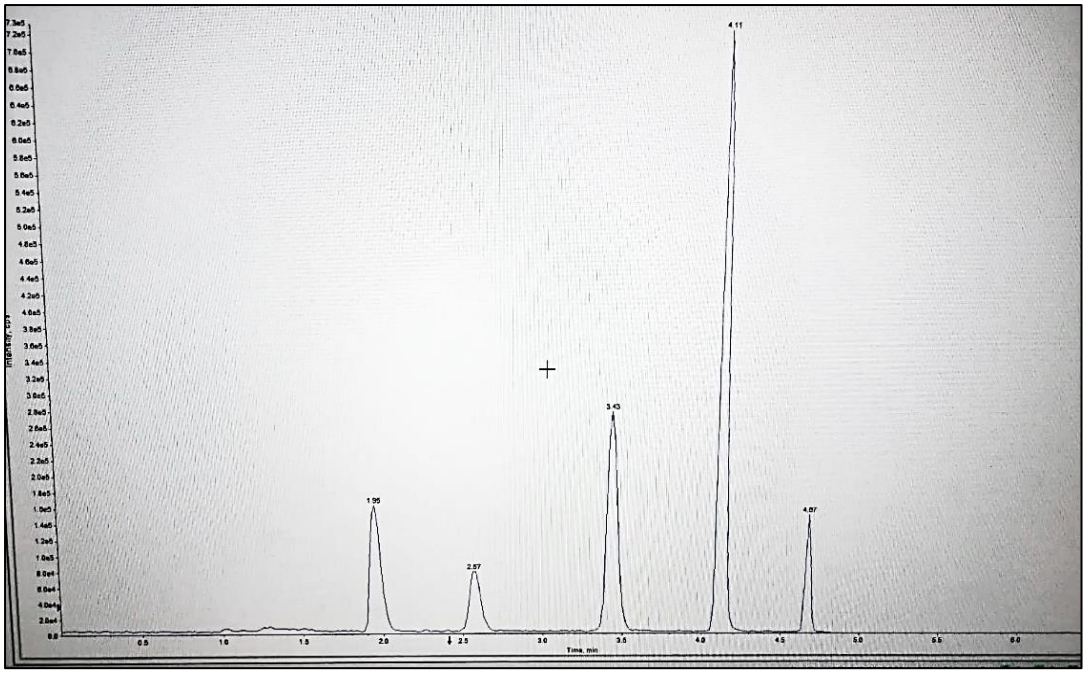

Figure 30: Emerging Contaminants Chromatogram, Order of Elution: Atenolol, Sulfamethoxazole, Nevirapine, Carbamazepine, and Efavirenz

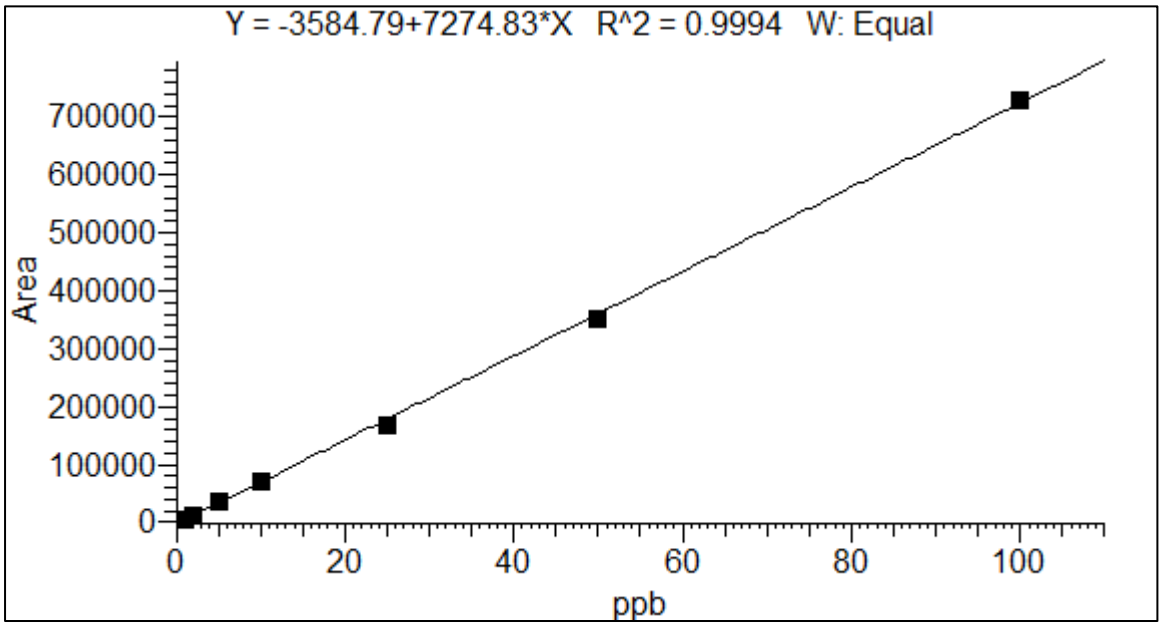

Figure 31: Chloroform Calibration Curve

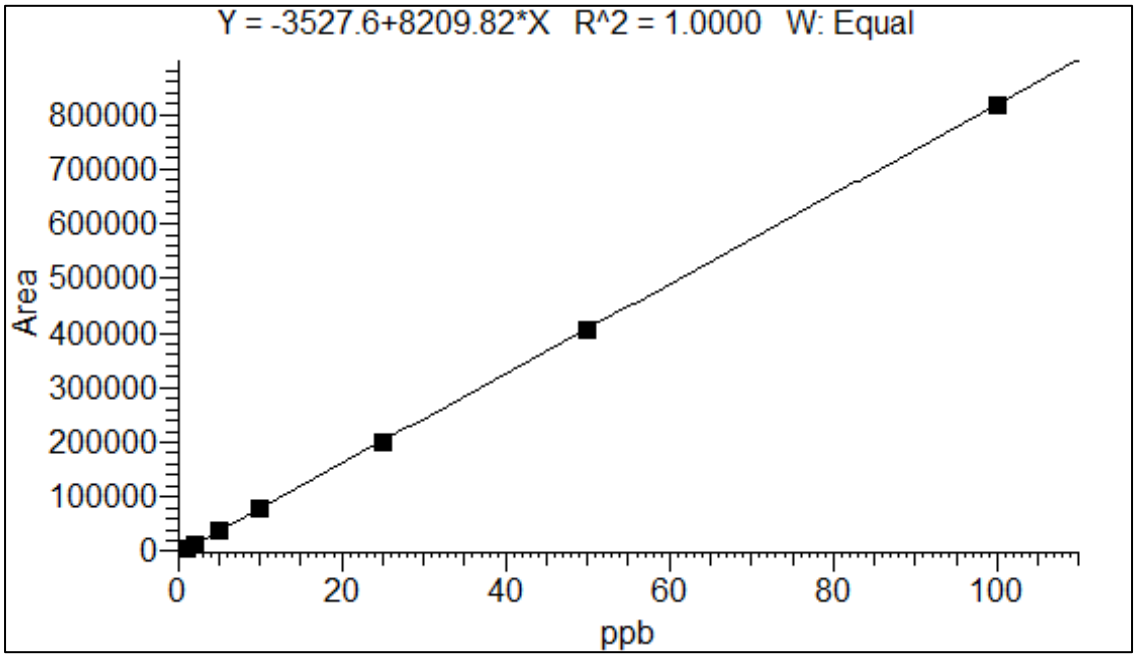

Figure 32: Dibromochloromethane Calibration Curve

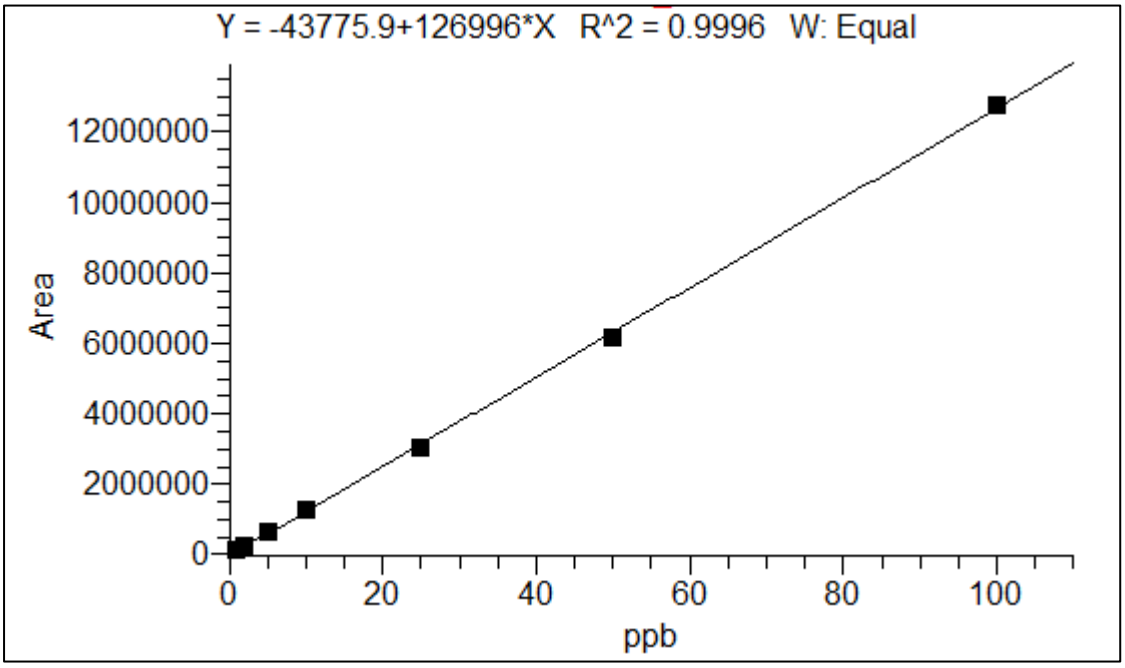

Figure 33: Bromoform calibration curve

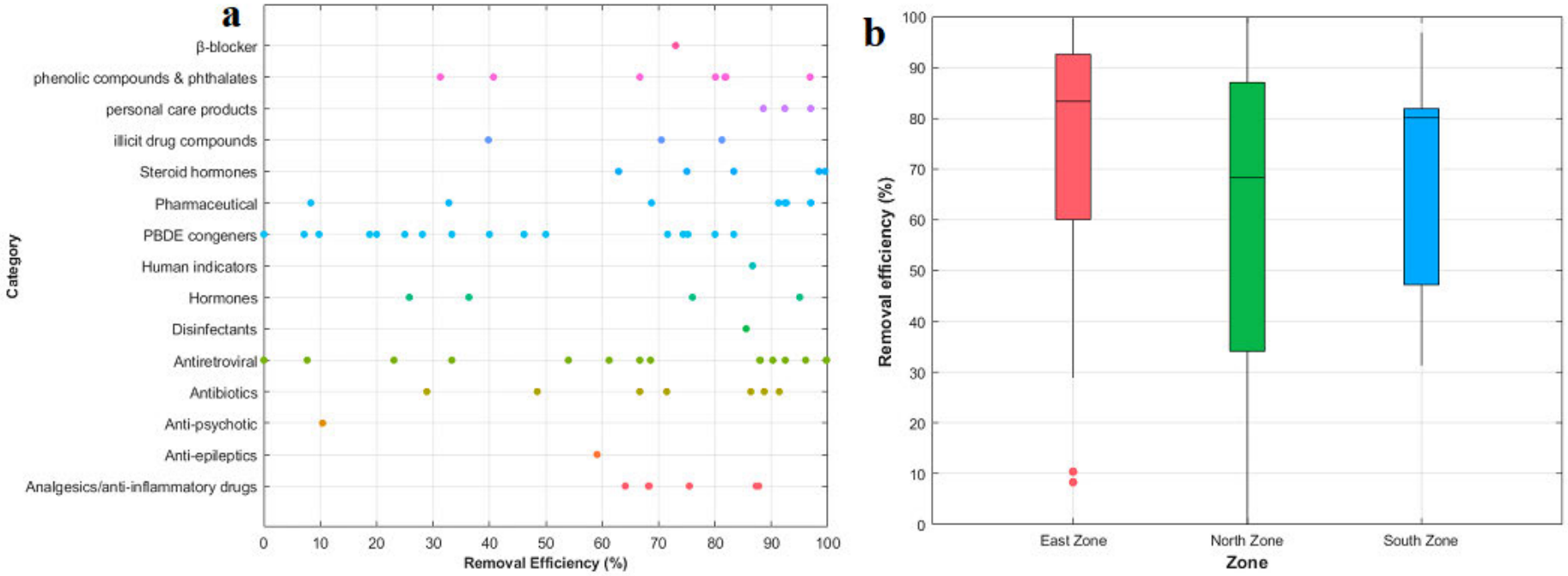

Figure 34: Percentage removal efficiency of ECs in WWTPs across South Africa. a) Compound category specific removal efficiencies. b) Median EC removal efficiencies of WWTPs in different zones of South Africa

The table provided above represents the publication output of my PhD research work, as extracted from the following source: Gani, K. M., Hlongwa, N., Abunama, T., Kumari, S. and Bux, F. 2021. "Emerging contaminants in the South African water environment: A critical review of their occurrence, sources, and eco-toxicological risks." Published in Chemosphere, Volume 269, and page 128737.