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# Occurrence and potential hazard posed by pharmaceutically active compounds in coastal waters in Cape Town, South Africa

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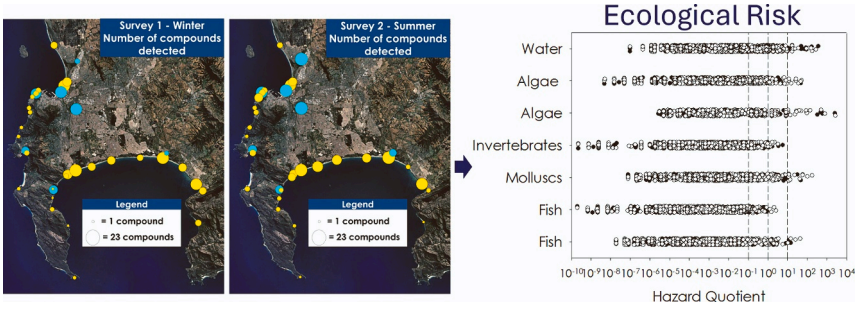
## HIGHLIGHTS

- Pharmaceutical pollution in river and coastal water in Cape Town was investigated.
- 58 pharmaceuticals were analysed in water sampled at 35 sites in summer and winter.
- At least one pharmaceutical was found in each sample.
- Salicylic acid was the most widespread PhAC
- Up to 22 pharmaceuticals were detected at some sites.

## GRAPHICAL ABSTRACT

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## ABSTRACT

The occurrence of 58 pharmaceutically active compounds (PhACs) in surface water at 28 coastal and five river sites, and in two stormwater flows in Cape Town, South Africa, was investigated in winter and summer. After accounting for quality assurance and control data, 33 PhACs were considered in detail. In winter, 25 PhACs were found at one or more sites and 27 in summer. Salicylic acid was the most widespread PhAC in each season. At least one PhAC was found at each site in each survey. The largest number found at a site was 22 at Lifebox23 Beach in winter and 23 at Macassar Beach and in the Black and Diep Rivers in summer. These sites are strongly directly or indirectly affected by wastewater treatment plant discharges. The range in ΣPhAC concentrations was

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Spatiotemporal variation
Environmental hazard

41 ng $L^{-1}$ to 9.3 μg $L^{-1}$ in winter and 109 ng $L^{-1}$ to 18.9 μg $L^{-1}$ in summer. The hazard posed by PhACs was estimated using Predicted No Effect Concentrations (PNEC) from several sources. Hazard Quotients (HQs) for numerous PhACs were >1, and for several even >10, including azithromycin, cimetidine, clarithromycin, erythromycin, and ibuprofen. The highest hazards were at coastal sites strongly indirectly affected by wastewater treatment plant discharges. Azithromycin, trimethoprim, and sulfamethoxazole at some sites may have promoted antibiotic resistance in bacteria, while irbesartan at some sites might have posed a hazard to fish according to the fish plasma model. The concentrations of several PhACs at some coastal sites are higher than concentrations reported in estuarine, coastal, and marine waters in other parts of the world.

## 1. Introduction

Modern society has benefitted from the discovery and production of pharmaceutically active compounds (PhACs) that aid in the diagnosis, treatment, and prevention of illnesses and diseases in humans and animals. PhACs are not fully metabolised in the human body and are excreted in faeces and urine (Jjemba, 2006). Topically applied PhACs are also washed from the human body surface during bathing. In this way they enter wastewater treatment plants (WWTPs) in communities connected to this infrastructure. Conventional WWTPs are not designed to remove PhACs from wastewater, which to varying degrees remain in treated wastewater discharged into surface waters (Kasprzyk-Hordern et al., 2009; Oulton et al., 2010; Yang et al., 2017). WWTP discharges are the primary pathway for PhACs into the environment in many countries (Petrović and Barceló, 2007; Kasprzyk-Hordern et al., 2009; Petrović et al., 2009; Gaw et al., 2014). In many least developed and developing countries, a large proportion of the population live in informal settlements in cities and rural areas with limited or no connection to sewer infrastructure. In these situations, PhACs enter the environment directly in human waste. Other pathways for PhACs into the environment, which are generally considered to be less important in terms of loads than WWTP discharges, include combined sewer system overflows, sewer leaks that infiltrate stormwater infrastructure, septic tanks, veterinary treatment of pets and livestock, pet and livestock waste, reclaimed wastewater used for irrigation, aquaculture operations, pharmaceutical manufacturing sites, and leachate migration from waste landfill sites (Holm et al., 1995; Kolpin et al., 2002; Watkinson et al., 2009; Phillips et al., 2010; Gaw et al., 2014; Launay et al., 2016; Masoner et al., 2015, 2019; Tran et al., 2019; Bastos et al., 2020; Wang et al., 2022). Recreational users of surface waters, such as swimmers and surfers urinating in water or releasing topically applied PhACs, are a further but probably insignificant source compared to most other sources.

The consequence of the aforementioned sources is that PhACs are essentially ubiquitous in groundwater, rivers, estuaries, and seawater in and near urban areas, and often further afield, raising concerns on their potential impacts to non-target biota (Hughes et al., 2013; Godoy et al., 2015; aus der Beek et al., 2016; Prichard and Granek, 2016; Čelić et al., 2019; Letsinger et al., 2019; Branchet et al., 2021; Wang et al., 2022; Archer et al., 2023). PhACs have been found in a range of freshwater, estuarine, and marine biota, including algae, molluscs, echinoids, and fish (Dodder et al., 2014; Fabbri and Franzellitti, 2016; Moreno-González et al., 2016; Fonseca et al., 2021; Ojemaye and Petrik, 2021; Mello et al., 2022). PhACs have been shown to induce a range of adverse effects in biota (Corcoran et al., 2010; Prichard and Granek, 2016; Fabbri and Franzellitti, 2016; Ortúzar et al., 2022). There are also concerns that antibiotic residues might interfere with the structure and functioning of microbial communities (Zhang et al., 2021; Świacka et al., 2023) and promote antibiotic resistance (Bengtsson-Palme and Larsson, 2016; Gaw et al., 2014).

WWTPs and sewer infrastructure in large parts of South Africa are in a parlous state, which results in raw or poorly treated wastewater regularly polluting rivers, estuaries, and coasts in many parts of the country. The South African Department of Water and Sanitation uses a so-called Green Drop programme to evaluate the performance of WWTPs in the country. A large proportion of the 995 WWTPs audited in 2021 performed poorly, with almost 40 % being classified as essentially dysfunctional. WWTPs in Cape Town achieved an overall score of 88 % in the audit (DWS, 2022). Since conventional WWTPs are not designed to remove PhACs from wastewater, they remain in treated wastewater discharged into surface waters in Cape Town (Archer et al., 2017, 2021, 2023). In Cape Town, as in other South African cities, the challenge is exacerbated by a large proportion of the population living in informal settlements that have no connection to sewer infrastructure. The communities rely largely on pit latrines, chemical toilets, or open discharge into rivers and the stormwater system, constituting a further source of PhACs to surface waters (Archer et al., 2020, 2023; Madikizela et al., 2022).

PhAC contamination of aquatic ecosystems in Africa has received far less attention than in other parts of the world (Hughes et al., 2013; aus der Beek et al., 2016; Waleng and Nomngongo, 2022; Madikizela et al., 2022). Most studies to date have focussed on freshwater ecosystems, predominantly in South Africa. Few studies have focused on PhACs in estuarine, coastal, and marine waters in Africa, studies in South Africa again being more prevalent than elsewhere on the continent (Waleng and Nomngongo, 2022). A few studies have investigated the prevalence of a small suite of PhACs in seawater, sediment, algae, invertebrates, and fish in the coastal and marine environment in parts of Cape Town (Petrik et al., 2017; Ojemaye and Petrik, 2019; Ojemaye and Petrik, 2021). However, a spatially extensive nor comprehensive study on PhACs has yet to be performed in the city's coastal waters, nor indeed in any other coastal city in South Africa.

The aim of this study was to improve the understanding on PhACs in coastal waters in South Africa, and more specifically in Cape Town. The prevalence, distribution, and potential environmental hazard posed by 58 PhACs in water sampled at 28 coastal sites, in five rivers, and in the flows from two stormwater pipes was investigated in winter and summer. To the best of our knowledge, this is the most comprehensive study on PhACs in coastal waters in Africa to date and provides the first records for numerous PhACs in surface waters on the continent.

## 2. Materials and methods

### 2.1. Chemicals and materials

Pharmaceutical standards (Table S1 in the Supporting material (SM)) were high purity grade (>90 %), purchased from Sigma-Aldrich (Steinheim, Germany), US Pharmacopeia, and European Pharmacopeia. Isotopically labelled compounds, used as internal standards (ISs), were atenolol-d7, azithromycin-d3, carbamazepine-d10, cimetidine-d3, citalopram-d4, diazepam-d5, erythromycin-N,$N^{13}C2$, fluoxetine-d5, ofloxacin-d3, phenazone-d3, sulfamethoxazole-d4, venlafaxine-d6, bezafibrate-d6, furosemide-d5, gemfibrozil-d6, hydrochlorothiazide-d2, ibuprofen-d3, indomethacine-d4, meloxicam-d3, and valsartan-d8. These were purchased from Sigma-Aldrich and Toronto Research Chemicals (Ontario, Canada). Isotopically labelled compounds used as surrogate standards were sulfadimethoxine-d6, sulfadoxine-d3, and ketoprofen-d3.

Individual stock standards (ISs), and surrogate solutions were prepared on a weight basis in methanol (1000 mg $L^{-1}$) except ofloxacin and ciprofloxacin, which were dissolved in methanol by adding 100 μL of 1

M NaOH and cefalexin, which was dissolved in high performance liquid chromatography (HPLC) grade water. After preparation, standards were stored at −20 °C. Antibiotic stock solutions (macrolides, sulphonamides, and trimethoprim) were prepared every three months, while cephalosporin and quinolone antibiotics were prepared monthly due to their limited stability. Stock solutions for other substances were renewed every six months. A mixture containing all PhACs was prepared by appropriate dilution of individual stock solutions in methanol-water (10:90 *v*/v). Working standard solutions were renewed before each analytical run. A separate mixture of ISs, used for internal standard calibration, and surrogates were also prepared in methanol and further diluted in methanol-water (10:90 v/v for water).

The cartridges used for solid phase extraction (SPE) were Oasis hydrophilic-lipophilic-balanced (HLB) sorbent (200 mg, 6 mL), from Waters Corporation (Milford, MA, USA). Glass fibre filters (GFF) and polyvinylidene fluoride (PVDF) filters were from Whatman (UK) and Merck Millipore (Darmstadt, Germany). HPLC grade methanol, acetonitrile, water (LiChrosolv), and formic acid 98 % were from Merck (Darmstadt, Germany). Ammonium hydroxide, hydrochloric acid, and ethylenediaminetetraacetic acid disodium salt solution (Na2EDTA) at 0.1 M were from Panreac. Nitrogen for drying was from Abelló Linde S. A. (Spain), and was of 99.9 % purity. A Milli-Q-Advantage system from Millipore Ibérica S.A. (Spain) was used to obtain HPLC-grade water.

### 2.2. Sampling sites and sample collection

Cape Town is in the southwestern part of South Africa. The area has a Mediterranean climate characterised by warm dry summers and cool wet winters. The area between Bloubergstrand and Diaz Beach is referred to in this study as the Atlantic Seaboard despite the city's entire coast bordering the Atlantic Ocean (Fig. 1). False Bay is a large south facing bay demarcated by Cape Point in the west and Cape Hangklip in the east. Effluent from 17 WWTPs of varying sizes, and six smaller facilities that use various treatment technologies is transported to the coast via rivers or outlets into the sea. Preliminary treated wastewater that accounts for ~7 % of the total daily wastewater production in Cape Town is discharged into the sea through marine outfalls at Green Point, Camps Bay, and Hout Bay on the Atlantic Seaboard, and at Robben Island in Table Bay (Fig. 1). Industrial wastewater from a private petroleum company is discharged into Table Bay through an outfall at Milnerton in Table Bay.

Grab water samples were collected in August 2021 (winter survey) and December 2021 (summer survey) at 35 sites (Fig. 1). Most sites (28) were on the coast (coastal sites), covering most of Cape Town's 307 km coastline. Five sites were in rivers and two were at surface runoff (stormwater) discharge points onto the shoreline. At coastal sites, water was sampled by wading into the surf zone and collecting a sample from


**Fig. 1.** Sites where surface water was sampled in Cape Town.

just below the water surface using a 2 L high-density polyethylene jug. The jug was also used to collect water at stormwater discharge points. In rivers, water was sampled from bridges using a plastic bucket attached to a rope. Prior to filling, jugs and buckets were sprayed with acetone and rinsed with ambient water several times. Sample storage containers were 500 mL high-density polyethylene bottles. Prior to fieldwork, the bottles were soaked overnight in 10 % nitric acid, rinsed with deionised water, sprayed internally with acetone, rinsed with deionised water and then ultrapure water, and air dried under clean aluminium foil. Two sample containers were filled per site, one for PhAC analysis and the other for faecal indicator bacteria analysis. A third sample container was filled at five sites for quality assurance and quality control purposes. Water samples for PhAC analysis were frozen at −18 °C in the laboratory, while those for faecal indicator bacteria analysis were refrigerated at 4 °C overnight.

### 2.3. Faecal indicator bacteria analysis

*E. coli* were analysed using a membrane filtration method. Samples were vacuum filtered through a membrane filter. The filters were incubated on a modified mFC agar medium at 44.5 ± 0.2 °C for 24 h and then on a nutrient agar medium containing MUG for 2 h at 35 ± 0.5 °C. The filters were examined under UV light and positive fluorescing colonies were enumerated. Faecal enterococci were also analysed using a membrane filtration method. The filters were incubated on m-enterococcus agar at 35 ± 0.5 °C for 48 h. The filters were examined, and colonies enumerated. Presumptive positive colonies were catalase tested and gram stained to confirm they were faecal enterococci.

### 2.4. PhAC analysis

#### 2.4.1. Sample preparation

The water samples were analysed for 58 PhACs from 13 therapeutic groups using a multi-residue method described by Gros et al. (2012). Briefly, samples were filtered through 1 μm GFF, followed by 0.45 μm PVDF membrane filters. Different sample volumes were used depending on the matrix, such as 100 mL for freshwater (river, stormwater) and 250 mL for seawater. A suitable volume of a 0.1 M $Na_2EDTA$ solution was added to the water samples to achieve a final concentration of 0.1 % (g solute/g solution). Water samples were spiked with an appropriate volume of a standard mixture containing surrogate standards, to have a concentration of 20 ng $L^{-1}$ in all samples type. SPE was conducted using Oasis HLB (200 mg, 6 mL) cartridges. Cartridges were previously conditioned with methanol (5 mL) and HPLC water (5 mL). After sample enrichment, SPE cartridges were rinsed with 6 mL of HPLC grade water at a flow rate of 2 mL $min^{-1}$ and then dried for 5 min to remove remaining water. Elution was conducted with 6 mL of pure methanol at a flow rate of 1 mL $min^{-1}$. Extracts were evaporated to dryness under a gentle nitrogen stream (>99.9 %) using the nitrogen evaporator ReactiTherm III Heating Module (TS-18824) (Thermo Fisher Scientific, Driesch, Germany) and reconstituted to 1 mL with a final proportion of methanol/HPLC-grade water (10:90, *v*/v). Finally, 20 μL of a 1 ng $L^{-1}$ standard mixture containing all isotopically labelled standards was added to the extract as an IS.

#### 2.4.2. Instrumental analysis

Sample extracts and analytical blanks were analysed by ultra-performance liquid chromatography (UPLC), using a Waters Acquity Binary Solvent Manager system (Waters Corporation, MA, USA) coupled to a 5500 QTRAP (Applied Biosystems, Foster City, CA, USA), a quadrupole linear ion trap tandem mass spectrometer ($QqLIT^-$) with a Turbo Ion Spray source, following the method developed by Gros et al. (2012). For chromatographic separation, 5 μL were injected in an Acquity HSS T3 column (50 mm × 2.1 mm i.d., 1.8 μm particle size) for positive electrospray ionization (PI), while an Acquity BEH $C_{18}$ column (50 mm × 2.1 mm i.d., 1.7 μm particle size) was used for the compounds analysed under negative electrospray ionization (NI). Both columns were purchased from Waters Corporation. Mobile phases used were methanol and 10 mM formic acid/ammonium formate (pH 3.2) for the analysis in PI mode, at the flow rate of 0.5 mL $min^{-1}$, whereas for the analysis in the NI mode, acetonitrile, and 5 mM ammonium acetate/ammonia (pH = 8) was used at the flow rate of 0.6 mL $min^{-1}$. For quantitative and detection purposes, two Selected Reaction Monitoring (SRM) transitions were monitored. All data was acquired and processed using SCIEX 2.1 software.

#### 2.4.3. Quality assurance and quality control

Eight-point calibration curves (0.1–100 μg $L^{-1}$) were generated using linear regression analysis. The calibration standard was measured repeatedly at the beginning and the end of each sequence and throughout the sequence, after every 10 injections, to check for signal stability. R-squared values were consistently >0.99 for all PhACs. Method and instrumental blanks were analysed to account for background levels of the analytes investigated. Field collected seawater and freshwater samples were spiked in triplicate with a known concentration of target analytes to determine recoveries of each analyte. The measured concentrations after the analytical process were compared to the initial spiking concentrations, calculated by internal standard calibration. Blanks (non-spiked samples) were also analysed and the concentrations found were subtracted from those obtained from spiked samples. The spiking concentration for all analytes was 20 ng $L^{-1}$. Spiked water samples were used to determine the limit of detection (LOD) and limit of quantification (LOQ). LOD and LOQ were established as the minimum detectable amount of analyte with a signal-to-noise ratio of 3 and 10, respectively. Quantification of the samples was based on peak areas and was performed by the internal standard calibration approach. For each compound, its corresponding isotopically labelled analogue was used apart from those substances whose corresponding labelled compound was not available. In this case, the most similar labelled substance in terms of chemical structure and chromatographic retention time was used (Čelić et al., 2021).

### 2.5. Statistical analysis

Statistical analyses and graphing were performed using Microsoft Excel® and SigmaPlot® v15 software. PhAC concentrations <LOQ or <LOD were not considered in analyses unless otherwise stated. The number of PhACs >LOQ and their total concentration was compared between sites on the Atlantic Seaboard and in False Bay using a Mann-Whitney *U* test since the data was not normally distributed (Shapiro-Wilk test).

### 2.6. Hazard assessment

#### 2.6.1. Hazard quotients

The environmental hazard posed by PhACs was estimated using Hazard Quotients (HQs), calculated as HQ = MEC/PNEC, where MEC is the measured environmental concentration and PNEC is the Predicted No Effect Concentration. HQs were classified as negligible hazard - HQ ≤0.1, low hazard −0.1 > HQ ≤1, medium hazard - 1 > HQ ≤10, and high hazard - HQ >10 (Mendoza et al., 2015; Canle and Antão-Geraldes, 2023). If a PhAC was >LOQ in at least one sample, concentrations reported as <LOD or < LOQ were replaced with a surrogate concentration equal to their value as a worst-case scenario. PhACs <LOD or < LOQ in all samples were not considered (acridone, diclofenac, metoprolol, norfluoxetine, ranitidine, sertraline).

HQs were calculated using PNECs for water, algae, invertebrates, and fish from several sources, for comparative purposes (Kuzmanović et al., 2015; Minguez et al., 2016; Norman Network Ecotoxicology Database). Acute toxicity data for freshwater biota provided by Kuzmanović et al. (2015) were used to derive PNECs by dividing the $EC_{50}$ by an Assessment Factor of 1000 for river and stormwater sites and 10,000 for

coastal sites, following European Chemicals Agency (2008) guidance. PNECs from Bengtsson-Palme and Larsson (2016) and Tell et al. (2019) were used to estimate the potential for promoting antibiotic resistance in microbial communities.

#### 2.6.2. Fish plasma model

The chronic hazard posed by PhACs to fish was estimated using the 'fish plasma model' proposed by Huggett et al. (2003). The model assumes molecular drug targets are conserved in humans and fish and pharmaceuticals will thus interact with targets in fish to cause a target-mediated pharmacological response in the same way as in humans (Meador et al., 2017). The model generates a Concentration Ratio (CR) as CR = CEC/MEC, where CEC is the Critical Environmental Concentration that should theoretically elevate the plasma concentration in fish to the same level as a human therapeutic plasma concentration and MEC is the measured environmental concentration of a PhAC. CECs were taken from Fick et al. (2010). In its original formulation, if CR is $\leq$1 the plasma concentration in exposed fish is equal to, or higher than the concentration known to cause a pharmacological response in humans. To simplify matters, the formula was inverted so CR $\geq$1 is indicative of a pharmacological response. CRs were classified as CR <1: low to negligible hazard, 1 $\leq$ CR <10: medium hazard, and CR $\geq$10: high hazard.

## 3. Results and discussion

### 3.1. Faecal indicator bacteria

*E. coli* and faecal streptococci bacteria were found at most sites in winter and summer, at up to 300,000 and 10,000 cfu 100 $mL^{-1}$ respectively (Fig. S1 and Table S3 in the SM). The counts, and hence wastewater/sewage influence was typically higher at river sites and in stormwater flows than at coastal sites. The counts at some coastal sites were nevertheless high in one or both surveys. The counts for both bacteria were inexplicably low in the Diep River in winter considering the high counts recorded in summer and the known poor water quality in this river. The flow in the final 10 km of the river before the coast consists largely of effluent from the Potsdam WWTP and numerous pollution sources discharging through stormwater infrastructure as opposed to natural river water, due to the excessive abstraction in the catchment to support agriculture.

Water quality at coastal sites in False Bay was generally poorer than on the Atlantic Seaboard, but at most sites water quality in each survey was nevertheless classified excellent for bathing according to South African guidelines. This is contrary to the findings of longer-term coastal water quality monitoring by the Cape Town municipality (CoCT, 2023), which has shown poorer water quality but is based on the analysis of results generated weekly over a 365-day rolling period rather than once-off seasonal sampling as in this study.

### 3.2. PhACs

#### 3.2.1. PhACs considered

PhACs with recoveries $\geq$50 % and $\leq$130 % and good repeatability (RSD $\leq$25 %) in seawater and freshwater matrices were considered apart from acetaminophen, hydrochlorothiazide, norfluoxetine, salicylic acid, and ranitidine in freshwater, which had recoveries or RSDs that did not meet one of the criteria (Table S2 in the SM). These PhACs were included to allow direct comparison amongst seawater and freshwater sites. Thirty-three PhACs were thus considered. The results for the other 25 PhACs are qualitative. Seven of these 25 PhACs were < LOD in all samples. Other PhACs were >LOD at 1–8 sites in winter and 1–16 sites in summer. Their inclusion would generally not have had a pronounced influence on trends. At 24 sites in each survey, their inclusion would have added $\leq$2, but mostly no additional PhACs, at a maximum additional total concentration of 43 ng $L^{-1}$. However, their inclusion would have added up to 14 PhACs at a maximum additional total concentration 1.7 μg $L^{-1}$ at river sites, eight PhACs at a maximum additional total concentration of 3.2 μg $L^{-1}$ at stormwater sites, and ten PhACs at a maximum additional total concentration of 1.2 μg $L^{-1}$ at coastal sites.

#### 3.2.2. PhAC detection

In winter, 25 (76 %) of the 33 PhACs considered were found at one or more sites compared to 27 (82 %) in summer (Fig. S2 in the SM). Twenty-five of the 33 PhACs were common to both surveys. Salicylic acid was the most prevalent PhAC, found at 32 of the 35 sites in winter and at all sites in summer. Other PhACs that found frequently ($\geq$12 sites) included acetaminophen, atenolol, bezafibrate, codeine, ofloxacin, sulfamethoxazole, trimethoprim, and valsartan (Fig. S2 in the SM). Several of the PhACs that were found frequently are amongst the most often prescribed pharmaceuticals in the public and/or private health care sectors in South Africa (Osunmakinde et al., 2013).

At least one PhAC was found at each site in each survey (Fig. 2). In winter, the largest number found was 22 at Lifebox23 Beach, while in summer it was 23 at Macassar Beach and in the Black and Diep Rivers. Apart from the stormwater pipe at Three Anchor Bay, sites with the highest diversity of PhACs were in rivers or near river mouths and canal outlets that receive effluent from WWTPs (Fig. S3 in the SM).

More PhACs were found at 22 sites in summer and at nine sites in winter, with no difference at four sites (Fig. S2 in the SM). At 24 sites, the seasonal difference was small ($\leq$3 PhACs). The largest difference was in the Diep River, where 19 more PhACs were detected in summer than in winter. The difference corresponds to far higher counts of faecal indicator bacteria at this site in summer (Fig. S1 in the SM), suggesting a stronger wastewater influence.

The median number of PhACs found at coastal sites in each survey and for the surveys combined was higher in False Bay (8.5) than on the Atlantic Seaboard (4), but the average was not significantly different amongst these areas (Mann Whitney $U$ test, $p > 0.05$). Nevertheless, this points to more significant contamination of coastal waters in False Bay, which is supported by the results of microbiological analysis of coastal water samples (CoCT, 2021; Fig. S1 in the SM).

Some coastal sites are remote from significant PhAC sources (e.g., WWTPs, river mouths) and probably accounts for the low number of PhACs found at these sites. Nevertheless, even at Diaz Beach at Cape Point, which is arguably the site most remote from PhAC sources (Fig. 1), ofloxacin and salicylic acid were found in winter and salicylic acid in summer. At Kogel Bay, a remote site on the eastern shore of False Bay (Fig. 1), six PhACs were found in winter and one in summer. Ojemaye and Petrik (2021) also found PhACs in the water at each of eight sites that covered much of the False Bay coast, including Kogel Bay and a more remote site near Cape Hangklip (Fig. 1). The detection of PhACs at remote sites alludes to the dispersion of wastewater contaminants over considerable distances along the Cape Town coast. Other sites where few PhACs were found were situated in more urbanised parts of Cape Town and nearer potential PhAC sources. The infrequent detection of PhACs at these sites might reflect the oceanographic and meteorological conditions prevailing at the time of the surveys rather than the long-term status since faecal indicator bacteria monitoring has revealed significant (but sometimes only periodic) wastewater/sewage related impairment of water quality at certain of the sites (e.g., Fish Hoek Beach, Simonstown Long Beach) (CoCT, 2023). The influence of oceanographic conditions on PhAC dissipation at Clifton 4th Beach, Camps Bay Beach, and Llandudno Beach on the Atlantic Seaboard is considered significant given a marine outfall discharges wastewater offshore of Camps Bay and Clifton 4th Beaches, and wastewater from a bioreactor is discharged near Llandudno. The low number of PhACs found at Simonstown Long Beach is surprising considering treated effluent is discharged to the nearshore ~800 m from the site. More frequent sampling at this and other sites might provide a different perspective on PhAC prevalence.

#### 3.2.3. PhAC concentrations

The Σ PhAC concentration range was 41 ng $L^{-1}$ to 9.4 μg $L^{-1}$ in

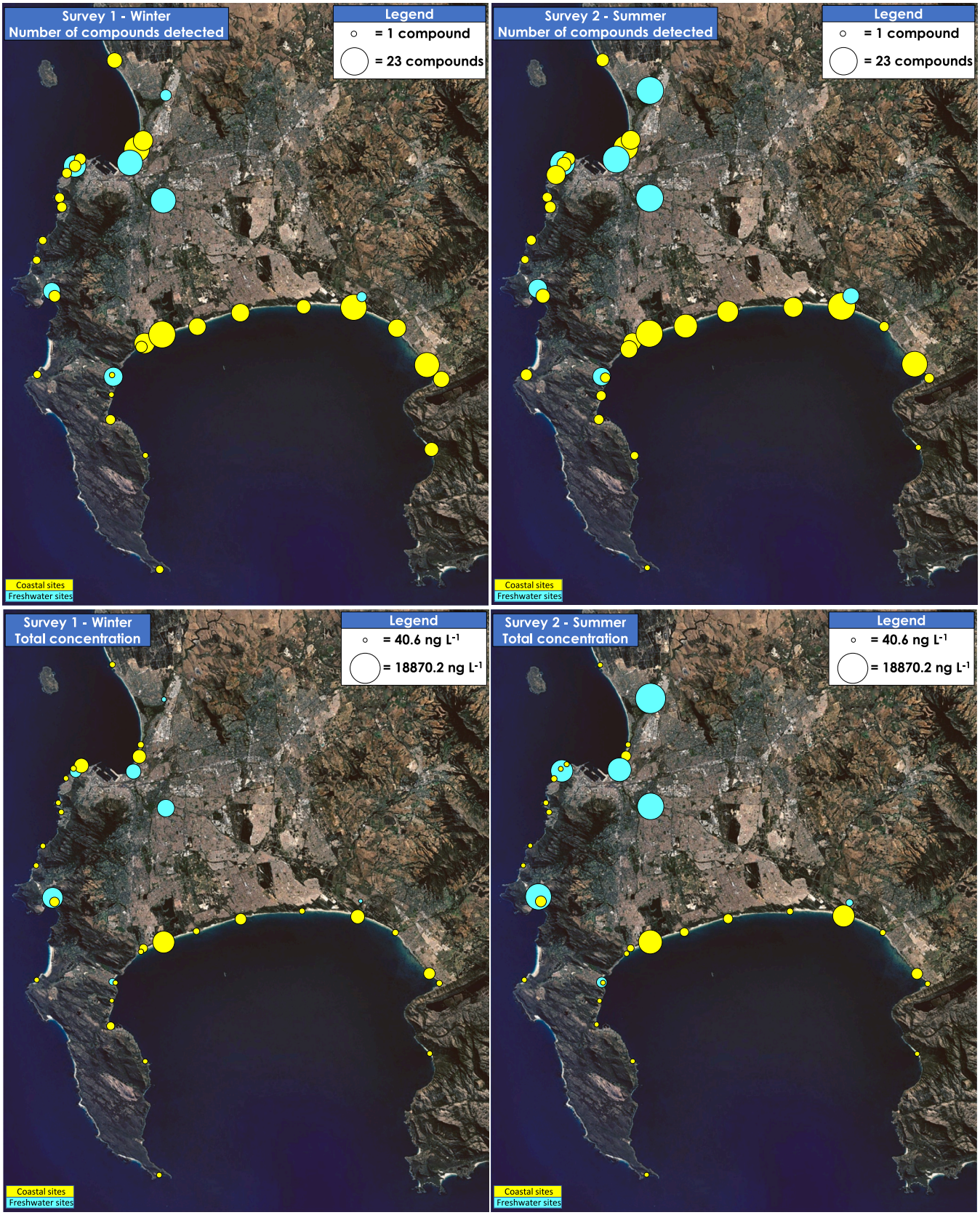


**Fig. 2.** The number of pharmaceutically active compounds found at a quantifiable concentration and the total concentration of these compounds in surface waters sampled in Cape Town.

winter and 109 ng $L^{-1}$ to 18.9 μg $L^{-1}$ in summer (Fig. 2, Table S3 in the SM). Acetaminophen, valsartan, and hydrochlorothiazide presented amongst the highest concentrations in each survey, with maxima of 5.8 μg $L^{-1}$, 0.4 μg $L^{-1}$, and 0.9 μg $L^{-1}$ in winter and 12.1 μg $L^{-1}$, 3.2 μg $L^{-1}$, and 2.3 μg $L^{-1}$ in summer, respectively. Eight other PhACs were recorded at a concentration > 1 μg $L^{-1}$ in summer, but in winter only salicylic acid was recorded at such a high concentration. Acetaminophen and salicylic acid contributed >50 % of the ΣPhAC concentration at 30 of the 35 sites in winter and at 24 sites in summer, these being mainly coastal sites (Fig. S3 in the SM). The highest concentrations for eight of the 25 PhACs found in winter and for 18 of the 27 PhACs found in summer were for a river or a stormwater site. The frequent detection and the high concentrations of ΣPhACs found at coastal sites near river mouths (e.g., Lagoon Beach, Macassar Beach, Strand Beach) underscores the importance of rivers as vectors for these compounds into coastal waters in Cape Town, which is consistent with the findings of studies in coastal cities in other parts of the world (Zhang et al., 2012; Ci et al., 2021). Stormwater is a vector for PhACs into aquatic systems in cities in other parts of the world (Petrović and Barceló, 2007; Birch et al., 2015; Launay et al., 2016; Fairbairn et al., 2018; Masoner et al., 2019; Tran et al., 2019; Yin et al., 2019; Fuchte et al., 2022) and was also the case for the stormwater flows at Three Anchor Bay and Fish Hoek Beach in Cape Town. PhACs were generally more prevalent and at a higher concentration in the stormwater flows than at coastal sites (Fig. 2). The presence of PhACs and faecal indicator bacteria in the stormwater flows implies sewage has infiltrated the stormwater infrastructure, probably via sewage infrastructure leaks and pump failures (overflows) and/or inadvertent or illegal cross connections between sewage and stormwater infrastructure. Dense informal settlements and high levels of homelessness in Cape Town probably also contribute to the pollution of stormwater flows. There was a generally strong similarity in the sites where amongst the lowest or the highest ΣPhAC concentrations were found in each survey. The prevalence and high (survey relative) concentrations of PhACs at many sites undoubtedly reflects pseudo-persistence due to the continuous release of treated wastewater from WWTPs into surface waters in Cape Town. The migration of PhACs in surface and subsurface flows from informal settlements with pit latrines is probably an additional source.

The generally higher prevalence and concentrations of PhACs at coastal sites in False Bay is probably explained by the higher dilution and dispersion potential in the sea on the more exposed Atlantic Seaboard and the higher volume of treated wastewater released into False Bay. Outfalls at Green Point, Camps Bay, and Hout Bay on the Atlantic Seaboard (Fig. 1) discharge preliminary treated wastewater some distance off the coast, which promotes the dilution and dispersion of wastewater contaminants. In contrast, no outfalls extend far offshore in False Bay. Treated wastewater and wastewater contaminated river flows thus enter False Bay via the surf zone more so than on the Atlantic Seaboard. Contaminants trapped in surf zones can be dispersed alongshore over large distances until they are transported into deeper water by rip currents or are diluted to extinction (Grant et al., 2005; Grimes et al., 2021; Zimmer-Faust et al., 2021), which might contribute to the generally higher prevalence and concentrations of PhACs at coastal sites in False Bay.

The difference in the ΣPhAC concentration between the summer and winter surveys was large (>1 μg $L^{-1}$) at ten sites, typically being higher in summer. The largest differences were in rivers and stormwater flows, although the difference at some coastal sites was also wide (Fig. 2). The reason for the large seasonal differences at some sites is uncertain but in the rivers, lower flows in summer (dry season) will have resulted in WWTP discharges not being diluted to the same degree as during higher flows in winter.

## 4. Hazard assessment

### 4.1. Hazard quotients

Generally, >95 % of the HQs for all sites and for coastal sites only are <1 (low hazard), regardless of the PNEC source; 68.4 % to 95.7 % of HQs are in fact <0.1 (negligible hazard) (Fig. 3). HQs >1 (medium risk) and >10 (high risk) are evident for each PNEC source apart from invertebrates and fish when calculated using PNECs from Kuzmanović et al. (2015), for which none are >10. The highest incidence of HQs >1 is for algae calculated using PNECs from Minguez et al. (2016) and water calculated using PNECs from the Norman Network. The HQs for some PhACs are very high, exceeding 100 for water and invertebrates calculated using PNECs from the Norman Network and for algae using PNECs from Minguez et al. (2016). The highest HQ is 2667 for the clarithromycin concentration recorded in water sampled near the Gordon's Bay canal in False Bay, calculated using the PNEC for algae from Minguez et al. (2016). In contrast, the HQ for this clarithromycin concentration is 8.8. when computed using the PNEC for algae from Kuzmanović et al. (2015) and 3.4 when computed using the Norman Network PNEC for water, underscoring the importance of the PNEC in hazard estimates.

Some of the high HQs reflect the fact LOQs and/or LODs for azithromycin and clarithromycin exceed PNECs from Minguez et al. (2016) and the PNEC for azithromycin from the Norman Network. The marine algal PNEC for clarithromycin from Minguez et al. (2016) is much lower than those provided by other sources. If azithromycin and clarithromycin are not considered, ≤2.6 % of HQs for all sites and ≤2.7 % for coastal sites are >1 apart from water calculated using PNECs from the Norman Network, for which the HQ at 8.0 % of all sites and 9.3 % of coastal sites was >1.

The PhACs most responsible for HQs >1 using PNECs from Kuzmanović et al. (2015) are acetaminophen, azithromycin, cimetidine, clarithromycin, erythromycin, losartan, and sulfamethoxazole, more commonly for algae (2.6 %) than invertebrates (0.7 %) and fish (0.2 %). In the case of PNECs from Minguez et al. (2016) the PhACs most responsible for HQs >1 are azithromycin, clarithromycin, and fluoxetine. A considerable proportion of the HQs for clarithromycin are >10 (23 % in winter, 40 % in summer), of which numerous are also >100 (14 % in winter, 11 % in summer). Numerous PhACs return HQs >1 using Norman Network PNECs, most often for azithromycin, cimetidine, furosemide, ibuprofen, iopromide, and sulfamethoxazole. A small proportion of the HQs for acetaminophen and azithromycin are >100. HQs >1 for water (10.4 %) were more prevalent than for invertebrates (4.3 %) and fish (2.5 %).

The sites presenting the highest potential hazard, if not necessarily for each PNEC source, are those that are strongly directly or indirectly affected by discharges from WWTPs. HQs were generally considerably higher for coastal sites than for sites in rivers and stormwater flows even though PhAC concentrations were generally higher in rivers and stormwater flows, reflecting the lower PNECs for marine biota.

PhACs usually occur as mixtures in the aquatic environment and can interact in ways that increase their toxicity to a level greater than individually, although this is not always the case (Cleuvers, 2003, 2004; DeLorenzo and Fleming, 2008; Kortenkamp et al., 2009; Backhaus et al., 2011; Geiger et al., 2016; de Sousa et al., 2022). A cumulative hazard approach has been shown to generally have a high predictive power for the toxicity of PhAC mixtures with different modes of action (Backhaus, 2014). The cumulative HQ at a large proportion of sites in Cape Town is >1 and at many sites is >10 (Fig. 4). The highest cumulative HQ is 2672 for water sampled near the Gordon's Bay canal in False Bay, calculated using marine algal PNECs from Minguez et al. (2016). High HQs for algae calculated using PNECs from Kuzmanović et al. (2015) for erythromycin, for marine algae using the PNEC from Minguez et al. (2016) for clarithromycin, and for water, invertebrates, and fish using PNECs for azithromycin from the Norman Network contribute to the high

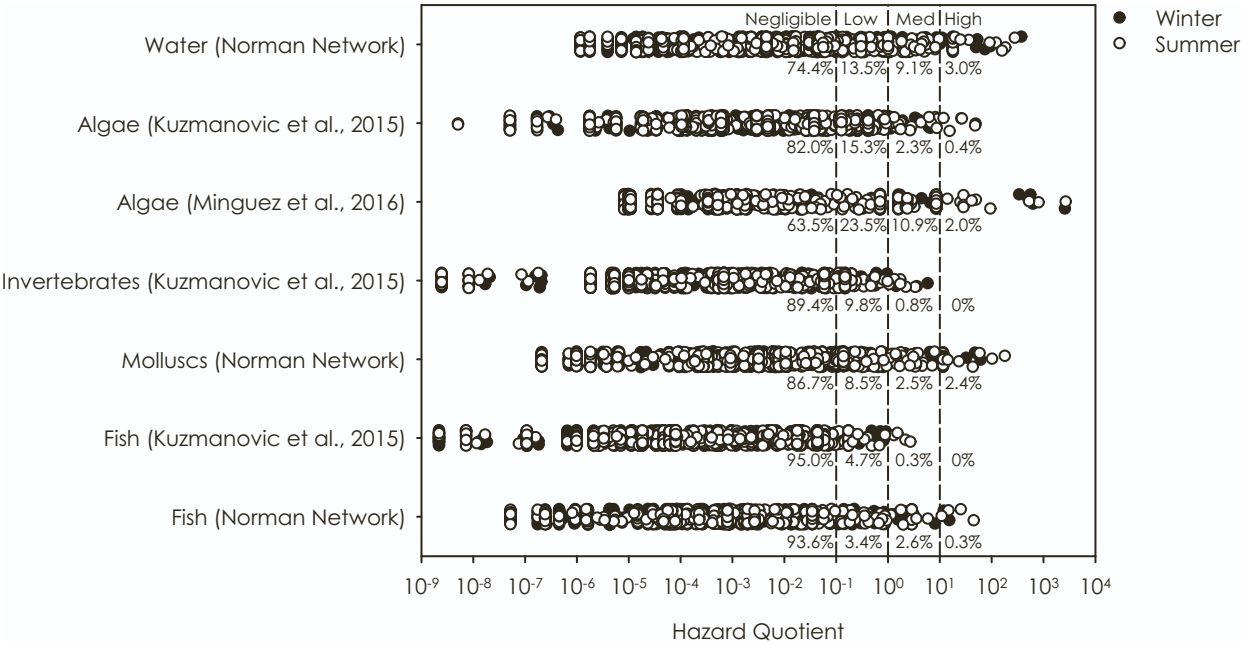


**Fig. 3.** Hazard Quotients calculated using Predicted No Effect Concentrations from various sources for pharmaceutically active compounds in surface waters in Cape Town.

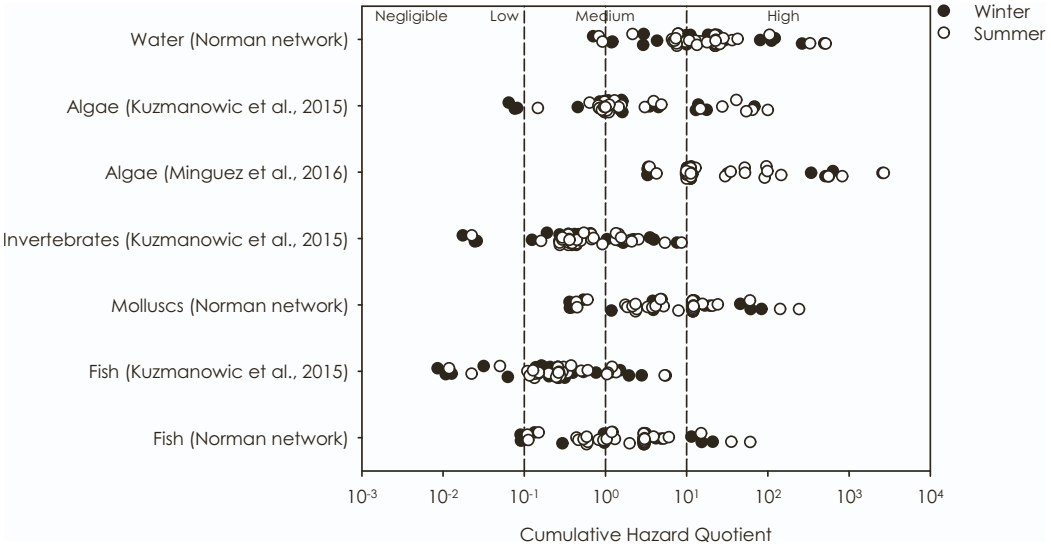


**Fig. 4.** Cumulative Hazard Quotients computed using Predicted No Effect Concentrations from various sources for pharmaceutically active compounds in surface waters in Cape Town.

cumulative HQs. The sites presenting the highest potential cumulative hazard, regardless of the PNEC source, are similar to those identified for individual PhACs. The potential hazard is considerably, and more frequently higher for water, algae, and invertebrates at Lagoon Beach, Lifebox23 Beach, and Macassar Beach than at other sites. PhACs that contribute importantly (≥25 %) to the cumulative HQ include azithromycin, losartan, sertraline, and to a lesser degree acetaminophen for HQs calculated using PNECs from Kuzmanović et al. (2015), clarithromycin for HQs calculated using PNECs from Minguez et al. (2016), and azithromycin, sertraline, and to a lesser degree ibuprofen for HQs calculated using PNECs from the Norman Network. If azithromycin and clarithromycin are not considered for the reasons given above, the proportion of cumulative HQs >10 decreases substantially and none computed using PNECs provided by Minguez et al. (2016) are >10. Nevertheless, for all PNEC sources a considerable proportion of the cumulative HQs are >1.

Apart from azithromycin in the Diep River and at Macassar Beach (highest HQ = 2.1), and trimethoprim in Hout Bay River and at Macassar Beach in summer, antibiotic concentrations were < PNECs for antibiotic resistance selection in bacteria provided by Bengtsson-Palme and Larsson (2016). Twenty-three azithromycin concentrations in winter and 21 in summer, and four sulfamethoxazole concentrations in summer were > PNECs from Tell et al. (2019). The highest HQ is 26. Nineteen azithromycin HQs > 1 in winter and 14 in summer reflect the fact the LOQ for seawater is 1.7 times greater than the PNEC. Nevertheless, four quantified azithromycin concentrations in winter and seven in summer exceed the PNEC and, combined with sulfamethoxazole, suggest a possible promotion of antibiotic resistance in bacteria.

The estimated hazard posed by PhACs in Cape Town surface waters depends strongly on the PNECs used to compute HQs. There are

similarities in the PhACs identified as posing the highest potential hazard using PNECs from different sources, but simultaneously differences due to the variation in PNECs for any PhAC and the number of PhACs for which PNECs are provided.

### 4.2. Fish plasma model

The fish plasma model estimates if a pharmacological response is likely in fish, but not the nature of the response. Although PHACs have beneficial effects in humans, their effects in fish are probably deleterious (Meador et al., 2017). The CR is <1 (low to negligible hazard) for all PhACs apart from irbesartan at one site in winter and six sites in summer (. Three of these sites are in rivers, the others being coastal sites. The highest CR is 16.8 (high hazard) for a site in the Diep River, in summer. Other HQs are ≤9.5 (medium hazard). It is uncertain if fish in Cape Town are exposed to irbesartan or other PhACs at concentrations and periods that promote bioaccumulation to a degree this reflects in plasma concentrations equalling or exceeding the CEC. To address this uncertainty, information on concentrations of PhACs the plasma of fish in Cape Town is required.

#### 4.2.1. Comparisons to other studies

The concentrations of numerous PhACs recorded at coastal sites in the winter and/or summer surveys are the highest, or amongst the highest compared to studies in other parts of the world, including salicylic acid, acetaminophen, hydrochlorothiazide, valsartan, sulfamethoxazole, bezafibrate, codeine, carbamazepine, iopromide, and cimetidine (Tables S5 and S6). The concentrations of other PhACs are amongst the lowest, including ibuprofen, trimethoprim, venlafaxine and numerous other PhACs that were not found at a quantifiable concentration.

Three studies reported on the prevalence and concentrations of acetaminophen, diclofenac, carbamazepine, sulfamethoxazole in coastal waters in Cape Town (Petrik et al., 2017; Ojemaye and Petrik, 2021; Ojemaye et al., 2023). These PhACs were found at a considerably higher frequency at comparable sites than in this study. Conversely, the highest concentrations recorded (1.88 ng $L^{-1}$ for acetaminophen, 1.56 ng $L^{-1}$ for carbamazepine, and 4.79 ng $L^{-1}$ for sulfamethoxazole; all in False Bay) were typically lower than the lowest quantified concentrations recorded in this study. The reason for the disparities is uncertain, particularly in False Bay where most sites sampled by Ojemaye and Petrik (2021) were in a similar position to sites sampled for this study, and many are strongly indirectly affected by WWTP discharges.

## 5. Conclusions

The findings of this study are consistent with studies in coastal cities in other parts in the world, which have also shown that PhACs are common and often ubiquitous contaminants in fresh and coastal waters. At some coastal sites in Cape Town the concentrations of numerous PhACs were higher, or amongst the highest when compared to concentrations reported in estuarine, coastal, and marine waters in other parts of the world. Comparative studies are required to properly understand the scale of PhAC contamination of coastal waters in other parts of South Africa considering wastewater management in many coastal towns and cities is poor. An appreciation of the hazard posed by PhACs in Cape Town surface waters depends on the source of the PNECs used to compute HQs, leading to uncertainty on the scale of potential toxic impacts of these compounds. The potential hazard posed by most PhACs is estimated to be negligible or low regardless of the PNEC source, but some might present a moderate or high hazard.

In less affluent countries, investments in advanced technologies that can remove or significantly reducing PhAC concentrations in wastewater often compete with and are relegated by other urgent developmental priorities, such as housing. Addressing the challenge of PhAC contamination in surface waters in these countries requires an emphasis on source-directed approaches, including controls, regulations, and incentives for pharmaceutical manufacturers, a transition toward prescribing fewer and less environmentally persistent and toxic PhACs, and mechanisms for the return of unused pharmaceuticals. Ultimately, humans must acknowledge their responsibility for PhAC contamination of surface waters and change their behaviour with regards to pharmaceutical use and disposal.

## CRediT authorship contribution statement

**Brent Kenneth Newman:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anisha Velayudan:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Diana Álvarez-Muñoz:** Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Mira Čelić:** Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Gregg Oelofse:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization. **Darryl Colenbrander:** Writing – review & editing, Investigation, Conceptualization. **Maria le Roux:** Writing – review & editing, Conceptualization. **Kuria Ndungu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Lawrence Mzukisi Madikizela:** Writing – review & editing, Funding acquisition. **Luke Chimuka:** Writing – review & editing. **Heidi Richards:** Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Brent Newman reports financial support was provided by City of Cape Town. Co-authors are in the employment of the City of Cape Town, which partly funded the research (Gregg Oelofse, Darryl Colenbrander, and Maria le Roux).

First and second authors (Brent Newman and Anisha Velayudan, through the CSIR) acted on a consultancy basis to the City of Cape Town for part of the research.

Other authors declare they have no competing financial interests or personal relationships that could influence the work reported in this study. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data is included as Supplementary Material in Supplementary Material.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.174800.

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