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Suspect screening to support source identification and risk assessment of organic micropollutants in the aquatic environment of a Sub-Saharan African urban center

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ABSTRACT

Organic micropollutants (OMPs) are contaminants of global concern and have garnered increasing attention in Africa, particularly in urban and urbanizing areas of Sub-Saharan Africa (SSA). In this work, we coupled suspect screening enabled by liquid chromatography-high-resolution mass spectrometry (LC-HRMS) with multivariate analysis to characterize OMPs in wastewater, surface water, and groundwater samples collected from Kampala, the capital and largest city of Uganda. Suspect screening prioritized and confirmed 157 OMPs in Kampala samples for target quantification. Many OMPs detected in Kampala samples occurred within concentration ranges similar to those documented in previous studies reporting OMP occurrence in SSA, but some have never or rarely been quantified in environmental water samples from SSA. Hierarchical cluster analysis established the source-related co-occurrence profiles of OMPs. Partial least squares regression and multiple linear regression analyses further pinpointed the concentration of nitrate and the content of a fluorescent organic matter component with excitation/emission maxima around 280/330 nm as predictors for the sample-specific cumulative concentrations of OMPs, suggesting the likely contribution of diffuse runoff and wastewater discharges to OMP occurrence in the aquatic environment of Kampala. Parallel calculations of exposure-activity ratios and multi-substance potentially affected fractions provided insights into the potential for biological effects associated with OMPs and highlighted the importance of expanded analytical coverage for screening-level risk assessments. Overall, our study demonstrates a versatile database-driven screening and data analysis methodology for the multipronged characterization of OMP contamination in a representative SSA urban center.

1. Introduction

Organic micropollutants (OMPs) refer to a broad spectrum of current use and emerging anthropogenic compounds (e.g., pharmaceuticals, pesticides, household chemicals, industrial additives) and their transformation products (TPs) that typically occur at ng/L to μg/L levels in aquatic systems (Escher and Fenner 2011; Schwarzenbach et al., 2006). Globally, the widespread occurrence of OMPs presents an ongoing challenge to water resources management due to concerns over their adverse impacts on environmental and human health (aus der Beek et al. 2016; Lukač Reberski et al. 2022; Malaj et al., 2014; Stehle and Schulz 2015; Wilkinson et al., 2022). Such concerns have become increasingly relevant in regions experiencing rapid population growth along with intensification of chemical production and use (Weiss et al., 2016) such as urban and urbanizing areas of Sub-Saharan Africa (SSA). Over the past decade, a growing number of studies have sought to characterize the occurrence, sources, and ecotoxicological risks of OMPs in Africa (Fekadu et al., 2019; Gwenzi and Chaukura 2018; K'Oreje et al., 2020; Madikizela et al., 2017; Ssebugere et al., 2020). Many OMPs identified in the African aquatic environment occur at concentrations comparable to those reported in North America, Europe, and Asia-Pacific (K'Oreje et al., 2020), but certain categories of OMPs (e.g., antivirals, anthelmintics, antimalarials, estrogens) have been detected at elevated levels (Adeola and Forbes 2022; Belew et al., 2021; Fekadu

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et al., 2019; Wilkinson et al., 2022) due to differences in the prevailing public health conditions, substance consumption patterns, and waste management practices among regions. Collectively, these earlier investigations establish a sound knowledge base regarding the types and levels of OMPs commonly found in African waters and advocate for collaborative research initiatives and capacity building to inform mitigation strategies in regions at risk.

To date, the majority of OMP occurrence studies in Africa have focused their efforts on the application of target analysis to quantify a preselected set or specific groups of OMPs informed by local monitoring priorities and available historical data. Very few studies have incorporated database-driven screening approaches enabled by high-resolution mass spectrometry (HRMS) to broaden the analytical coverage for a more holistic assessment of OMP contamination status in African aquatic systems. To the best of our knowledge, K'oreje and colleagues (K'Oreje et al., 2012) were among the first to combine drug consumption data with liquid chromatography-HRMS (LC-HRMS) for suspect screening of pharmaceuticals in water samples collected from the Nairobi River basin of Kenya. More recently, (Kandie et al., 2020; Madikizela et al., 2022) applied suspect screening using self-curated compound lists to complement their target quantification of OMPs in water samples collected from the Lake Victoria South Basin in Kenya and the Klip River catchment in South Africa, respectively. Wood et al., 2017; Hu et al., 2021; Huff Chester et al. 2022, on the other hand, leveraged vendor-supplied compound databases to pursue suspect or nontarget screening of OMPs in water samples from South Africa, Nigeria, and Ghana, respectively. Such studies shed light on the potential of HRMS screening for prioritization and identification of less targeted OMPs in the African environment beyond those routinely flagged for target analysis. However, only a handful of suspect or nontarget OMPs identified in these studies were ultimately quantified by authentic reference standards, thus preventing further evaluation of their environmental impacts.

This work aims to combine suspect screening enabled by LC-HRMS with multivariate analysis to support source identification and risk assessment of OMPs in the aquatic environment of a representative SSA urban center – Kampala, Uganda. Like other cities in the African Great Lakes region, Kampala has witnessed fast population growth and significant urban expansion (Forget et al., 2021; Richmond et al., 2018) and is facing complex environmental challenges that are further exacerbated by socioeconomic disparities and climate variability (Li et al., 2021; Twinomuhangi et al., 2021). For example, only a small fraction of the population in Kampala is served by sewage treatment plants, whereas the remaining population relies on onsite sanitation facilities such as septic tanks and pit latrines or open drainage channels for domestic waste disposal (McConville et al., 2019; O'Brien et al., 2017). Furthermore, the population in high-income neighborhoods typically has access to piped water supply, but the population residing in informal settlements has a high reliance on groundwater from springs or harvested rainwater for domestic (e.g., drinking and cooking) and other uses (Byrne et al., 2021; Nayebare et al., 2014). Several recent studies have documented the occurrence of perfluoroalkyl substances (Arinaitwe et al., 2021; Dalahmeh et al., 2018), pharmaceuticals (Dalahmeh et al., 2020; Nantaba et al., 2020; Twinomucunguzi et al., 2021), and other OMPs such as pesticides, personal care products, plasticizers, and flame retardants (Nantaba et al., 2021; Twinomucunguzi et al., 2021) in Kampala, although the number of OMPs quantified in each study was limited.

Our specific objectives of this study were (i) to perform suspect screening and target quantification of OMPs in wastewater, surface water, and groundwater samples collected from Kampala; (ii) to compare the concentration ranges of OMPs measured in Kampala samples to those previously reported for SSA; (iii) to explore the strength of water quality variables as predictors for the overall level of OMPs; and (iv) to evaluate the potential for biological effects associated with OMPs using two screening-level risk assessments.

2. Materials and methods

2.1. Field sampling

Over the course of this study (January 2018-July 2019), a total of 106 grab samples (2 L each; Table S2) were collected using pre-cleaned sampling bottles from sites within the urban and peri-urban areas of Kampala, Uganda (**Fig. 1**). Surface water samples were collected from the catchments of drainage channels (e.g., Nakivubo, Lubigi, Mayanja, Nalukolongo, Kinawataka, Kansanga) in Kampala (n = 45) and nearshore sites in the Murchison Bay of Lake Victoria (n = 13). Groundwater samples (n = 33) were collected from springs located in densely populated neighborhoods or informal settlements. Lastly, wastewater samples (n = 15) were collected from sites near the inlets and outlets of the two sewage treatment plants administered by the National Water and Sewerage Corporation. Care was taken to minimize unintended contamination during sample collection in compliance with trace-level sampling protocols (U.S. Geological Survey, 2006). Samples were transported to the laboratory at Makerere University on the same day of collection and stored under −20 °C until extraction. Field blanks (i.e., deionized water poured into sampling bottles, opened in the field, and brought back to the laboratory) were prepared for each sampling trip.

2.2. Sample analysis

Within 48 h of collection, thawed samples (duplicate; 500 mL each) were spiked with a mixture of isotope-labeled internal standards (ILIS; 200 ng/L each; Table S5), filtered through 0.7-μm glass fiber filters under vacuum, and extracted by preconditioned solid-phase extraction (SPE) cartridges packed with Sepra ZT (200 mg; Phenomenex), Sepra ZT-SAX (100 mg; Phenomenex), Sepra ZT-SCX (100 mg; Phenomenex), and ISOLUTE ENV+ (150 mg; Biotage) sorbents as the top layer and Enviro-Clean graphitized nonporous carbon (200 mg; United Chemical Technologies) as the bottom layer (Wang et al., 2020). SPE cartridges were wrapped in aluminum foil and shipped together with additional 100-mL filtered sample aliquots to Syracuse University for further processing within a week to minimize analyte losses. Upon arrival at the laboratory in Syracuse, filtered sample aliquots were analyzed for water quality-related physicochemical and optical properties (Table S3). SPE cartridges were eluted sequentially with 6 mL of methanol/ethyl acetate (50:50 v/v with 2% ammonia), 3 mL of methanol/ethyl acetate (50:50 v/v with 1.7% formic acid), and 2 mL of methanol (Wang et al., 2020). Sample extracts were concentrated to 0.1 mL by rotary evaporation and N_2 blowdown and reconstituted with methanol:water (10:90 v/v) to 1 mL prior to injection onto a Dionex UltiMate 3000 high-performance liquid chromatograph interfaced with a Thermo Scientific LTQ XL hybrid ion trap-Orbitrap high-resolution mass spectrometer for OMP analysis (Table S4). Chromatographic separation of OMPs was performed on a Hypersil GOLD C18 column (100 × 2.1 mm, 1.9 μm; preceded by a guard cartridge) running a binary gradient of water and methanol (modified with 0.1% v/v formic acid) at a flow rate of 200 μL/min and a column temperature of 35 °C. Mass spectrometric analysis was conducted in positive and negative electrospray ionization modes in separate runs. Full scan mass spectra were first acquired over the m/z range of 100 to 1000 with a mass resolution of 60,000 at m/z 400. Full scan triggered data-dependent tandem mass (dd-MS2) spectra were then acquired upon reinjection of sample extracts with a mass resolution of 7500 at m/z 400 using higher energy collision-induced dissociation while maintaining a full scan mass resolution of 30,000 at m/z 400. Field blanks were extracted by the same SPE method and analyzed with each batch of samples.

2.3. Suspect screening and target quantification

Suspect screening was conducted in *TraceFinder 4.1* (Thermo Scientific) using an in-house suspect database detailing compound-specific

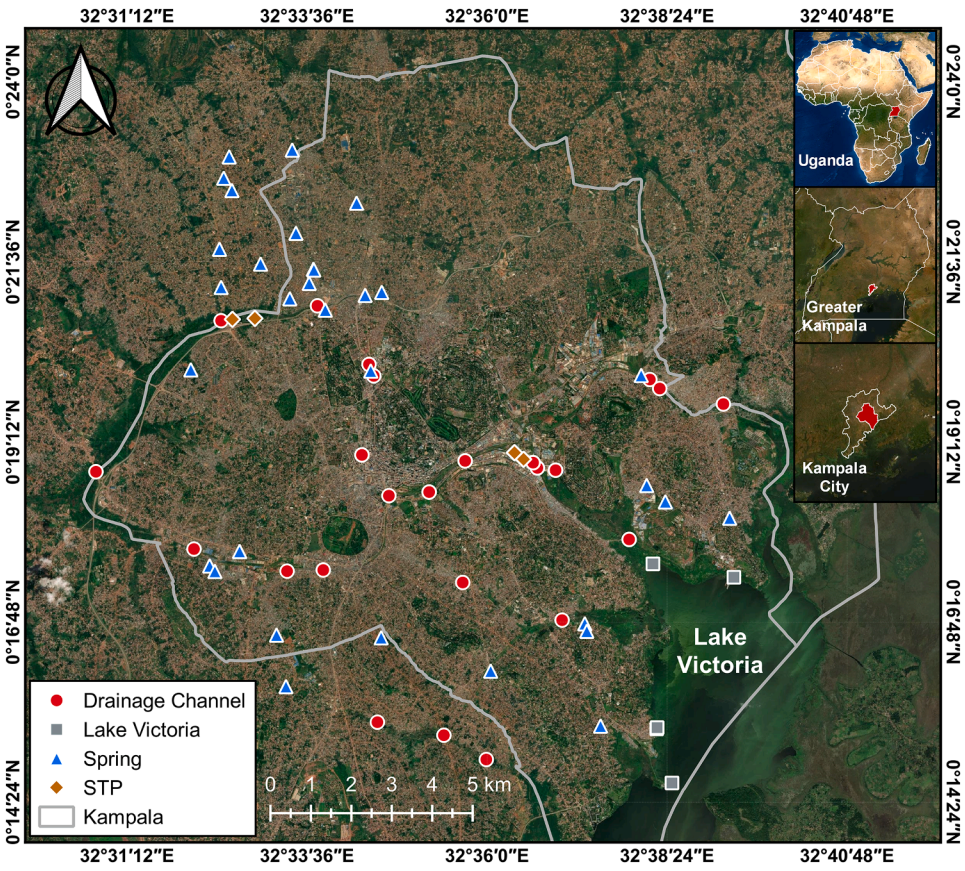


Fig. 1. Map of the sampling sites in Kampala, Uganda. The red circles represent the sampling sites on drainage channels. The gray squares represent the nearshore sampling sites in the Murchison Bay of Lake Victoria. The blue triangles represent the sampling sites at protected and unprotected springs. The brown diamonds represent the sampling sites near the inlets and outlets of the two sewage treatment plants (STPs) serving Kampala. Sampling dates and site coordinates are summarized in Table S2. Satellite Image Source: Esri, Maxar, GeoEye, Earthstar Geographics, CNES/Airbus DS, USDA, USGS, AeroGRID, IGN, and the GIS User Community.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

information (Table S14) for 1677 OMPs curated from the National Drug Register (National Drug Authority, 2019) and Agricultural Chemical Register of Uganda (Ministry of Agriculture Animal Industry and Fisheries, 2019) as well as prior studies reporting OMP occurrence in SSA aquatic systems. Compounds with a predicted Log*P* beyond the range of −2.0 to 6.0, containing only carbon and hydrogen atoms but no heteroatoms, or containing metallic or metalloidic elements were removed from the database. Full scan mass spectra were processed by *TraceFinder* with optimized peak picking parameters (Table S6) for suspect database matching to prioritize peaks for the acquisition of dd-MS2 spectra. Full scan triggered dd-MS2 spectra of suspect compounds were processed by *Compound Discoverer 3.3* (Thermo Scientific) for mass spectral library searching via *mzCloud* (HighChem LLC, 2022) and *MassBank* (MassBank-consortium and its contributors, 2020) using a node-based workflow (Table S7). Suspect compounds with a spectral match factor of >70 (n = 285; Table S8) were selected for further evaluation against authentic reference standards, among which 157 were confirmed by verification of their chromatographic retention times and dd-MS2 spectra.

Target quantification of 157 confirmed OMPs in samples was performed retrospectively using 12-point calibration curves. Twelve calibration standards (i.e., prepared in triplicate using 500 mL of ultrapure water spiked with the mixture of 157 OMPs at concentrations ranging from 0.1 to 3000 ng/L followed by the mixture of ILIS at 200 ng/L) were extracted and analyzed following the same SPE-LC-HRMS method described above. Calibration curves (R^2 = 0.995±0.005; n = 157; Table S9) were constructed in *TraceFinder* by the non-weighted linear least squares regression algorithm. Concentrations of OMPs were determined by comparing the peak area ratios of OMPs to their assigned ILIS (i.e., structurally identical ILIS or ILIS with the closest chromatographic retention times) in samples to the corresponding ratios in calibration standards. Calibration standards (for continuous verification) and solvent blanks (for carryover checks) were run with each sample sequence. Method reproducibility was monitored by the percent relative standard deviations (5.4 ± 3.5%; n = 101; Table S5) of the ILIS peak areas of calibration standards from all sample sequences. For each target OMP, the absolute SPE recovery, ion suppression or enhancement, matrix factor, and limits of quantification (Table S9) were determined as detailed in our previous work (Wang et al., 2020).

2.4. Data analysis

Following the screening and quantification of OMPs, hierarchical cluster analysis was performed using the *ComplexHeatmap* package (Gu et al., 2016) in *R 4.0.3* to visualize the source-related clustering patterns of OMPs based on their *z*-score standardized median quantifiable concentrations. Partial least squares regression (PLSR) analysis was performed with *SIMCA 17.0.2* (Umetrics) using the sample-specific cumulative concentrations of OMPs (Σ[OMPs]) as the response variables and a suite of water quality parameters (i.e., the concentrations of dissolved organic carbon, nitrate, chloride, bromide, and fluoride, the specific UV absorbance at 254 nm, and the maximum fluorescence intensity of four fluorescent organic matter components extracted by deconvoluting the excitation-emission matrices of samples with parallel factor analysis) as the predictor variables to rank their predictive power for Σ[OMPs]. Multiple linear regression was performed by stepwise variable selection to identify a subset of PLSR-prioritized water quality parameters that could best predict Σ[OMPs] with minimal multicollinearity. Two screening-level risk assessment methods were applied to evaluate potential for biological effects associated with OMPs. Exposure-activity ratios (EARs) were calculated for single OMPs with reliable exposure-effects relation data in the ToxCast database (U.S. Environmental Protection Agency's Center for Computational Toxicology and Exposure, 2021) using the *toxEval* package (De Cicco et al.

2020) in *R*. Potentially affected fractions (PAFs) of species for single OMPs were calculated by the species sensitivity distributions approach (de Zwart and Posthuma 2005) based on the log-transformed acute median toxicity (EC50) values for Multiple species and OMP combinations (Posthuma et al., 2019). For each sample, the sample-specific cumulative EARs (ΣEARs) and multi-substance potentially affected fraction (msPAF) for the mixture of OMPs were calculated by assuming concentration addition (Backhaus and Faust 2012; Blackwell et al., 2017) and response addition (de Zwart and Posthuma 2005), respectively. Other statistical analyses (e.g., Spearman's rank correlation analysis) were performed using *GraphPad Prism 8.4*.

3. Results and discussion

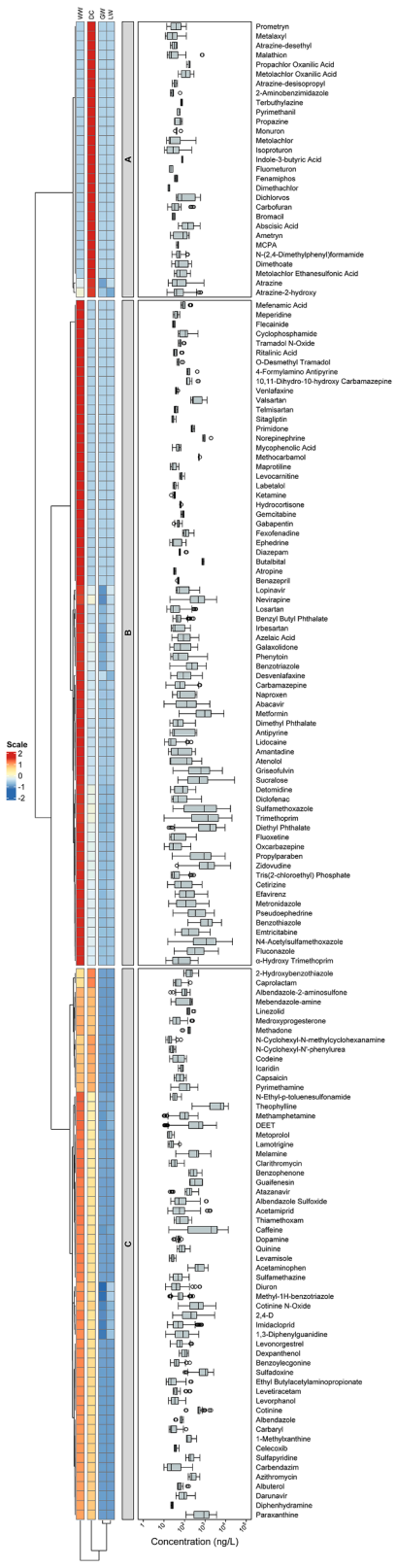
3.1. Occurrence patterns of OMPs in Kampala samples

Overall, 157 OMPs prioritized by suspect screening were confirmed and quantified in Kampala water samples with concentrations spanning the range of 10 to 27,300 ng/L (Table S10). Of the 157 OMPs quantified herein, 85 can be broadly classified as pharmaceuticals, 28 as pesticides, 20 as household chemicals and industrial additives, and 24 as TPs. One hundred of these OMPs occurred in both wastewater and drainage channel water samples, among which 26 were also detected at least once in nearshore lake water and groundwater samples, indicating the near-ubiquity of these OMPs in different aquatic compartments of Kampala. On average, the cumulative detections of OMPs in wastewater ($n = 96 \pm 15$) and drainage channel water samples ($n = 70 \pm 15$) were markedly higher than those in lake water ($n = 33 \pm 7$) and groundwater samples ($n = 12 \pm 6$). Similarly, the median Σ[OMPs] in wastewater (102,000 ng/L) and drainage channel water samples (27,600 ng/L) were at least one to two orders of magnitude higher than those measured in lake water (3540 ng/L) and groundwater samples (534 ng/L). Lastly, the sample-specific cumulative detection of OMPs (ranging from 5 to 124 with a median count of 52) exhibited a strong correlation (Spearman's $\rho = 0.959$; $p < 0.0001$) with Σ[OMPs] (ranging from 211 to 171,000 ng/L with a median value of 20,600 ng/L), which supports the relevance of both metrics for assessing the magnitude of OMP contamination. Furthermore, the concentrations of the six most frequently detected OMPs (i.e., caffeine, carbamazepine, efavirenz, fluconazole, nevirapine, and sulfamethoxazole) all showed strong positive correlations (Spearman's $\rho = 0.901$–0.965; $p < 0.0001$) with Σ[OMPs] and may serve as an abbreviated list of indicator compounds to infer the extent of OMP occurrence in Kampala samples.

To further explore the co-occurrence profiles of OMPs in relation to their potential sources, hierarchical cluster analysis was applied to the *z*-score standardized median quantifiable concentrations of 157 OMPs (**Fig. 2**), which revealed three clusters of OMPs based on Euclidean distance with Ward's method. Cluster A contains 29 OMPs that occurred at comparatively high median concentrations in drainage channel water samples, among which 21 are agricultural and mixed-use pesticides such as chloroacetanilides (e.g., dimethachlor and metolachlor), phenylureas (e.g., isoproturon and monuron), *s*-triazines (e.g., atrazine and prometryn), organophosphates (e.g., dichlorvos and malathion), and plant growth regulators (e.g., abscisic acid and indole-3-butyric acid). Eight remaining cluster A OMPs were pesticide TPs derived from chloroacetanilides and *s*-triazines (e.g., atrazine-2-hydroxy and metolachlor oxanilic acid), carbendazim (i.e., 2-aminobenzimidazole), and amitraz (i.e., *N*-(2,4-dimethylphenyl)formamide). Of the 29 cluster A OMPs, atrazine featured the highest detection frequency (i.e., 73%) and occurred at a median concentration (i.e., 27 ng/L) similar to that of atrazine-2-hydroxy (i.e., 30 ng/L), a TP with the second highest detection frequency (i.e., 64%). Atrazine and atrazine-2-hydroxy were detected in all sample matrices; however, other cluster A pesticides and pesticide TPs only occurred at varying concentrations in drainage channel water samples, indicating that these OMPs primarily originated from diffuse sources within the catchments of Kampala drainage networks.

Cluster B contains 70 OMPs that occurred at the highest median concentrations in wastewater samples. Fifty-four cluster B OMPs were various pharmaceuticals such as analgesics (e.g., antipyrine and detomidine), anesthetics (e.g., lidocaine and ketamine), antiallergics (e.g., cetirizine and fexofenadine), antibacterials (e.g., sulfamethoxazole and trimethoprim), antidepressants (e.g., desvenlafaxine and fluoxetine), antidiabetics (e.g., metformin and sitagliptin), antiepileptics (e.g., carbamazepine and phenytoin), antifungals (e.g., fluconazole and griseofulvin), antihypertensives (e.g., losartan and irbesartan), anti-inflammatories (e.g., diclofenac and naproxen), antivirals (e.g., nevirapine and efavirenz), and immunosuppressants (e.g., cyclophosphamide and mycophenolic acid). Fifteen of these pharmaceuticals (i.e., carbamazepine, cetirizine, desvenlafaxine, efavirenz, fluconazole, griseofulvin, irbesartan, lidocaine, losartan, metformin, metronidazole, nevirapine, sulfamethoxazole, trimethoprim, and zidovudine) had a relatively high detection frequency (i.e., 79±14%) and occurred at a wide range of median concentrations (i.e., 19–930 ng/L). Seven other cluster B OMPs were pharmaceutical TPs, including four (i.e., 10,11-dihydro-10-hydroxy carbamazepine, 4-formylamino antipyrine, α-hydroxy trimethoprim, and N4-acetylsulfamethoxazole) that co-occurred with their parent compounds at lower concentrations. Nine remaining cluster B OMPs were industrial additives (i.e., benzotriazole, benzothiazole, phthalates, and tris(2-chloroethyl) phosphate) and household chemicals (i.e., sucralose, galaxolidone (a TP of galaxolide), and propylparaben) that occurred at median concentrations (i.e., 29–880 ng/L) with a detection frequency (i.e., 79±7%) comparable to those measured for the 15 most frequently detected cluster B pharmaceuticals. Thirty cluster B pharmaceuticals and pharmaceutical TPs only occurred in wastewater samples, suggesting that they were exclusively derived from wastewater. Other 40 cluster B OMPs also occurred in drainage channel water, lake water, and/or groundwater samples, corroborating the high variability in OMP mixture composition among sample matrices and the contribution of both point and non-point source wastewater discharges in Kampala to OMP occurrence in receiving aquatic compartments.

Cluster C contains 58 OMPs that occurred at higher median concentrations in wastewater and drainage channel water samples than in lake water and groundwater samples. Thirty-one cluster C OMPs were pharmaceuticals such as analgesics (e.g., levorphanol and acetaminophen), anthelmintics (e.g., albendazole and levamisole), antibacterials (e.g., clarithromycin and sulfadoxine), antiepileptics (e.g., lamotrigine and levetiracetam), antiparasitics (e.g., pyrimethamine and quinine), antivirals (e.g., atazanavir and darunavir), bronchodilators (e.g., theophylline and albuterol), contraceptives (e.g., levonorgestrel and medroxyprogesterone), and stimulants (e.g., methamphetamine and caffeine). Eight other cluster C OMPs were pharmaceutical TPs derived from anthelmintics (e.g., albendazole), caffeine, cocaine, and nicotine, including four (i.e., 1-methylxanthine, paraxanthine, albendazole sulfoxide, and albendazole-2-aminosulfone) that co-occurred with their parent compounds. Nineteen remaining cluster C OMPs were seven pesticides (i.e., neonicotinoids, 2,4-D, carbaryl, carbendazim, and diuron) that are widely applied in urban and agricultural settings, eight industrial additives such as tire-derived chemicals (e.g., 1,3-diphenylguanidine, caprolactam, *N*-cyclohexyl-*N*-methylcyclohexanamine, *N*-cyclohexyl-*N'*-phenylurea), insect repellents (i.e., DEET, icaridin, and ethyl butylacetylaminopropionate), and benzophenone. Eleven cluster C OMPs (i.e., caffeine, methamphetamine, theophylline, cotinine, acetamiprid, imidacloprid, 2,4-D, diuron, 1,3-diphenylguanidine, methyl-1H-benzotriazole, and DEET) featured a comparatively high detection frequency (i.e., 73±9%) and occurred at median concentrations varying over an order of magnitude (i.e., 23–1510 ng/L). Five of these OMPs (i.e., caffeine, acetamiprid, imidacloprid, 2,4-D, and DEET) occurred in all sample matrices, whereas the remaining six OMPs were not detected in groundwater samples. Other less frequently detected cluster C OMPs occurred in wastewater and drainage channel water samples over a



(caption on next column)

Fig. 2. Hierarchical clustering of 157 OMPs by their *z*-score standardized median quantifiable concentrations in Kampala samples based on Euclidean distance with Ward's method. The color scale (red to blue) measures the detection frequency of OMPs. OMPs are grouped into three clusters (i.e., cluster A, B, and C, respectively). Cluster A is operationally designated as diffuse-source OMPs. Cluster B is operationally designated as wastewater-derived OMPs. Cluster C is operationally designated as mixed-source OMPs. The row annotations correspond to the quantifiable concentration ranges of OMPs (in the logarithmic scale). Each box extends from the 25th to 75th percentiles. The whiskers extend down to the 25th percentile minus 1.5 times of the interquartile range and up to the 75th percentile plus 1.5 times of the interquartile range. The centerline in each box marks the median. Points plotted beyond the whiskers are outliers. The column annotations correspond to specific sample matrices. "WW" represents wastewater samples (n = 15), "DC" represents drainage channel water samples (n = 45), "LW" represents nearshore Lake Victoria water samples (n = 13), and "GW" represents groundwater samples (n = 33), respectively. Concentration data of OMPs quantified in wastewater, surface water, and groundwater samples from Kampala are summarized in Table S10. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

narrower range of median concentrations. Such heterogenous occurrence patterns further support the hypothesis that a large portion of OMPs enters the aquatic environment of Kampala from mixed sources such as wastewater discharges, urban development, and agricultural activities.

3.2. *Comparative evaluation of OMP occurrence in Kampala and SSA*

Over the past decade, the environmental occurrence data of OMPs have become increasingly available for SSA countries, including those historically underrepresented in OMP research (K'Oreje et al., 2020; Wilkinson et al., 2022). To place results from this work in the context of existing literature, the geometric mean concentrations of OMPs quantified in Kampala samples were evaluated against data curated from prior studies reporting OMP occurrence in SSA wastewater, surface waters, and groundwater. Only data from studies that quantified OMP concentrations in aquatic matrices using liquid or gas chromatography-mass spectrometry were selected for comparison. Studies that extracted sludge, sediment, or biota samples, deployed passive sampling devices, or applied non-mass spectrometric methods for OMP analysis were excluded from further consideration. With these criteria, the mean concentrations of OMPs reported by 68 studies published up to March 2022 were compiled, resulting in a total of 1912 data entries (Table S11). To our knowledge, this is by far the most comprehensive OMP occurrence database ever assembled for aquatic samples from SSA. Seven of these 68 studies reported OMP concentrations in Ugandan samples, while the remaining collected data from 23 other SSA countries. Together, these 68 studies documented the occurrence of 349 unique OMPs in various types of environmental water samples (e.g., wastewater influent and effluent, river and stream water, lake and reservoir water, estuarine and coastal water, groundwater and drinking water) from SSA, among which 91 were also detected in samples from Kampala and the Ugandan waters of Lake Victoria (Arinaitwe et al., 2021; Dalahmeh et al., 2020; Dalahmeh et al., 2018; Nantaba et al., 2020, 2021; Twinomucunguzi et al., 2021). Over 90% of the data entries were mean concentrations reported for wastewater and surface waters (Figure S5), suggesting that the occurrence of OMPs in SSA groundwater only received limited attention.

Comparing the spectrum of OMPs quantified in this work to those reported in previous studies reveals that 69 of the 157 OMPs (i.e., 42 pharmaceuticals and pharmaceutical TPs, 15 pesticides and pesticide TPs, 9 industrial additives, and 3 household chemicals) have never been quantified in environmental water samples from SSA. Some of these OMPs have been widely (e.g., oxcarbazepine, isoproturon, sucralose, benzothiazole, melamine, methyl-1H-benzotriazole,) or increasingly (e.g., tire-derived chemicals) detected in wide-scope screening studies

conducted on other continents (Angeles et al., 2021; Carpenter and Helbling 2018; Emadian et al., 2021; Fabregat-Safont et al., 2021; Peter et al., 2018), whereas several are rarely studied compounds (e.g., benazepril, detomidine, maprotiline, albendazole sulfoxide, albendazole-2-aminosulfone, mebendazole-amine) with potentially high environmental relevance (Belew et al., 2021; Petrovic 2014). Sixty-one additional OMPs (i.e., 39 pharmaceuticals and pharmaceutical TPs, 18 pesticides and pesticide TPs, 2 industrial additives, and 2 household chemicals) have been detected at least once in other regions of SSA but not in Uganda. On average, the cumulative concentration of OMPs never quantified in Ugandan and/or SSA studies constituted 20–71% of Σ[OMPs] measured in Kampala wastewater, surface water, and groundwater samples, again demonstrating the added value of suspect screening for capturing less frequently detected or previously overlooked OMPs.

Of the 157 OMPs quantified in Kampala samples, 51, 68, and 11 overlapped with those previously detected in SSA wastewater, surface water, and groundwater samples, respectively (Fig. 3). Many of the overlapping OMPs occurred in Kampala samples at concentrations similar to those found in prior studies. For example, the geometric mean concentrations of 30 pharmaceuticals and pharmaceutical TPs (i.e., from 31 ng/L for lamotrigine to 6820 ng/L for sulfamethoxazole), benzotriazole (i.e., 649 ng/L), and propylparaben (i.e., 3840 ng/L) detected in 100% Kampala wastewater samples fell within the mean concentration ranges (multiple t tests $p = 0.537–0.591$) of these 32 OMPs measured in SSA wastewater (i.e., 25–6150 ng/L). Likewise, the geometric mean concentrations of 12 pharmaceuticals and pharmaceutical TPs (i.e., from 24 ng/L for lidocaine to 1650 ng/L for caffeine), 2,4-D (i.e., 240 ng/L), acetamiprid (i.e., 68 ng/L), and 3 phthalates (i.e., 43–1380 ng/L) detected in 100% drainage channel and nearshore lake water samples from Kampala also overlapped with the mean concentration ranges of these 17 OMPs reported for SSA surface waters (i.e., 10–1980 ng/L). Lastly, the geometric mean concentrations of carbamazepine (i.e., 26 ng/L) and sulfamethoxazole (i.e., 60 ng/L), the two OMPs detected in

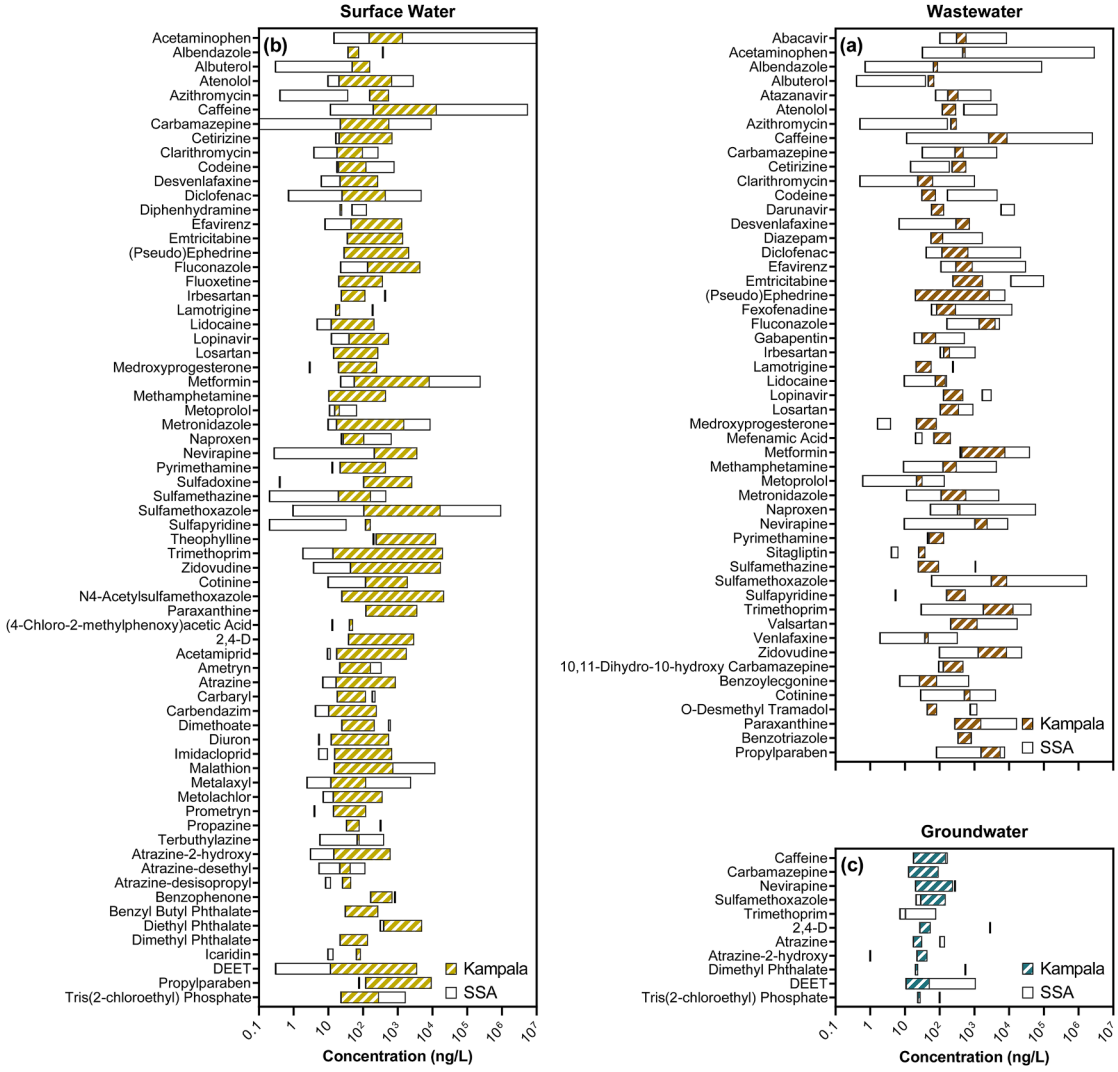


Fig. 3. Comparison of OMP concentration data measured in this work versus data collected from 24 countries in SSA: (a) Concentration ranges of 68 overlapping OMPs quantified in Kampala wastewater samples superimposed on the ranges of mean concentrations reported for SSA samples. (b) Concentration ranges of 51 overlapping OMPs quantified in Kampala surface water samples superimposed on the ranges of mean concentrations reported for SSA samples. (c) Concentration ranges of 11 overlapping OMPs quantified in Kampala groundwater samples superimposed on the ranges of mean concentrations reported for SSA samples. Each striped floating bar represents the quantifiable concentration range of a given OMP in Kampala samples. Each gray floating bar represents the range of mean concentrations of a given OMP reported for SSA samples in prior studies. Concentration data of OMPs reported for environmental water samples from 24 countries in SSA (i.e., Angola, Benin, Burkina Faso, Cameroon, Republic of the Congo, Democratic Republic of the Congo, Côte d'Ivoire, Ethiopia, Ghana, Kenya, Lesotho, Liberia, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, South Sudan, Tanzania, The Gambia, Uganda, Zambia, and Zimbabwe) are summarized in Table S11. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

100% Kampala groundwater samples, were not statistically different (multiple t tests p = 0.537–0.591) from the mean concentrations observed in SSA groundwater (i.e., 18–42 ng/L). Considering the spatiotemporal extent of studies compiled for evaluation, the similarity in concentration ranges indicates some consistency in OMP recurrence patterns throughout the aquatic environment of SSA.

Of the remaining overlapping OMPs detected in 100% Kampala samples, several occurred at concentrations above those measured in similar SSA sample matrices while others occurred at lower levels. For example, the geometric mean concentrations of medroxyprogesterone (i.e., 42 ng/L) and sulfapyridine (i.e., 247 ng/L) in Kampala wastewater samples far exceeded the mean concentrations measured in SSA wastewater (i.e., 3–5 ng/L); however, the geometric mean concentrations of emtricitabine (i.e., 543 ng/L), lopinavir (i.e., 194 ng/L), and sulfamethazine (i.e., 51 ng/L) were at least one order of magnitude lower than the mean concentrations detected in SSA wastewater (i.e., 1080–33,500 ng/L). Furthermore, the geometric mean concentrations of DEET (i.e., 411 ng/L) and propylparaben (i.e., 810 ng/L) in Kampala surface water samples were substantially higher than those reported for SSA surface waters (i.e., 20–77 ng/L), whereas the geometric mean concentration of tris(2-chloroethyl) phosphate (i.e., 40 ng/L) was 10 times lower than the mean concentration observed in SSA surface waters (i.e., 419 ng/L). Such heterogeneous profiles reflect the mixture complexity of OMPs across regions and reinforce the necessity of establishing statistically robust baseline levels to support adaptive OMP monitoring in SSA.

3.3. Water quality variables as predictors for OMP occurrence

Measuring water quality parameters provides complementary metrics for assessing site-specific OMP contamination status at the time of sample collection. For example, previous work characterizing the spatial distribution of pharmaceuticals in the Ugandan waters of Lake Victoria observed strong associations between pharmaceutical levels and water quality indicators such as turbidity (Nantaba et al., 2021). To evaluate the strength of water quality variables for predicting OMP occurrence in Kampala samples, PLSR analysis was performed using the sample-specific cumulative concentrations of cluster A, B, and C OMPs (i.e., $\Sigma[\text{OMPs}]_{\text{Cluster A}}$, $\Sigma[\text{OMPs}]_{\text{Cluster B}}$, and $\Sigma[\text{OMPs}]_{\text{Cluster C}}$) as the

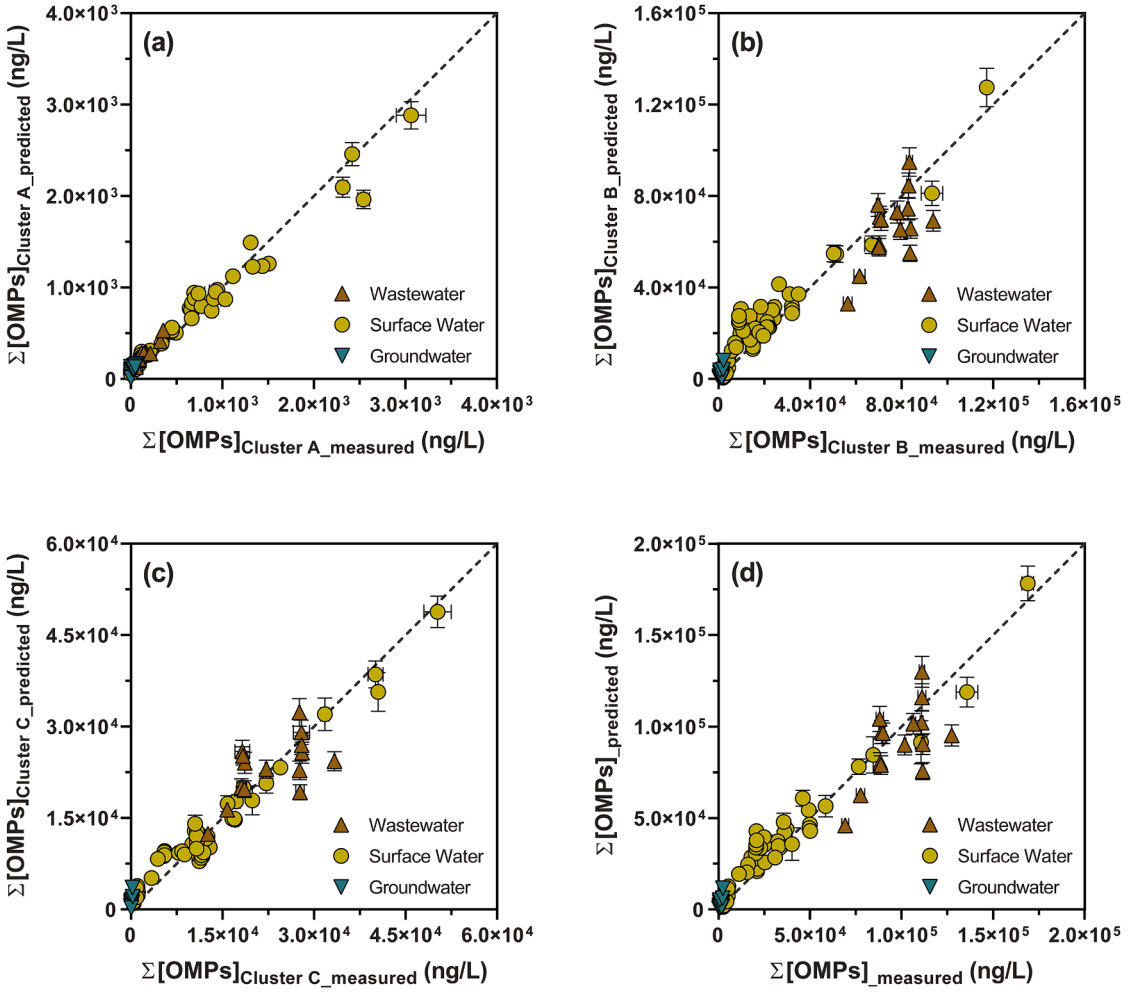


Fig. 4. Comparison of the measured versus predicted sample-specific cumulative concentrations of OMPs (Σ[OMPs]) in Kampala samples: (a) Cross plot of $\Sigma[\text{OMPs}]_{\text{Cluster A}}$ measured in Kampala samples (with the subscript "measured") versus $\Sigma[\text{OMPs}]_{\text{Cluster A}}$ predicted (with the subscript "predicted") by $\Sigma[\text{OMPs}]_{\text{Cluster A}} = 31.43(\pm0.58)\times[NO_3^-]$ (adjusted $R^2 = 0.953$) where $\Sigma[\text{OMPs}]_{\text{Cluster A}}$ is in the unit of ng/L and $[NO_3^-]$ is in the unit of mg/L. (b) Cross plot of $\Sigma[\text{OMPs}]_{\text{Cluster B}}$ measured in Kampala samples versus $\Sigma[\text{OMPs}]_{\text{Cluster B}}$ predicted by $\Sigma[\text{OMPs}]_{\text{Cluster B}} = 2800(\pm66)\times C4$ (adjusted $R^2 = 0.913$) where $\Sigma[\text{OMPs}]_{\text{Cluster B}}$ is in the unit of ng/L and C4 is in the unit of water Raman unit. (c) Cross plot of $\Sigma[\text{OMPs}]_{\text{Cluster C}}$ measured in Kampala samples versus $\Sigma[\text{OMPs}]_{\text{Cluster C}}$ predicted by $\Sigma[\text{OMPs}]_{\text{Cluster C}} = 918(\pm26)\times C4+179(\pm15)\times[NO_3^-]$ (adjusted $R^2 = 0.945$) where $\Sigma[\text{OMPs}]_{\text{Cluster C}}$ is in the unit of ng/L, C4 is in the unit of water Raman unit, and $[NO_3^-]$ is in the unit of mg/L. (d) Cross plot of Σ[OMPs] measured in Kampala samples versus Σ[OMPs] predicted by $\Sigma[\text{OMPs}] = 3807(\pm97)\times C4+126(\pm57)\times[NO_3^-]$ (adjusted $R^2 = 0.941$) where Σ[OMPs] is in the unit of ng/L, C4 is in the unit of water Raman unit, and $[NO_3^-]$ is in the unit of mg/L. Error bars indicate the standard deviation of measured Σ[OMPs] or the 95% confidence interval of predicted Σ[OMPs]; where absent, bars fall within symbols. The dark gray dashed line represents the line of identity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

response variables and 11 physicochemical and optical properties of water samples as the predictor variables. Overall, the strength of explained variation (i.e., 95.4 ± 1.9%) and the goodness of cross-validated prediction (i.e., 92.9 ± 2.9%) for the PLSR model were high, suggesting that the predictor variables adequately captured the inter-sample variability in Σ[OMPs]. On the basis of the variable importance in the projection scores (Figure S6), the concentration of nitrate (i.e., [NO_3^-]) and the maximum fluorescence intensity of a protein-like fluorescent organic matter component (i.e., C4; with excitation/emission maxima around 280/330 nm; Figures S3-S4) commonly present in wastewater or wastewater-impacted aquatic systems (Hudson et al., 2007) were ranked as the two variables with the highest explanatory power.

Recognizing the multicollinearity among predictor variables, stepwise multiple linear regression analysis was further performed to identify the most parsimonious models for predicting Σ[OMPs]. Specifically, [NO_3^-] and C4 were single variables that could effectively predict $\Sigma[OMPs]_{Cluster\ A}$ and $\Sigma[OMPs]_{Cluster\ B}$, respectively, whereas C4 and [NO_3^-] served as the best combination of predictors for $\Sigma[OMPs]_{Cluster\ C}$ (**Fig. 4**). Furthermore, the inclusion of additional predictor variables for Σ[OMPs] did not significantly improve model consistency with measured data. The fact that C4 emerged as a strong predictor for $\Sigma[OMPs]_{Cluster\ B}$ and $\Sigma[OMPs]_{Cluster\ C}$ reaffirms the vulnerability of Kampala surface waters and groundwater to OMP contamination associated with wastewater inputs. Interestingly, an earlier study assessing the occurrence of pharmaceuticals in the Nairobi River catchment in Kenya also attributed elevated pharmaceutical concentrations in surface waters to wastewater influence based on the concurrent measurements of protein-like organic matter content using fluorescence spectroscopy, although no direct quantitative relationships were identified (Bagnis et al., 2020). On the other hand, nitrate has long been viewed as a continental-scale diffuse source contaminant in Africa with a high potential to pollute surface waters and infiltrate shallow groundwater (Lapworth et al., 2017; Ouedraogo and Vanclooster 2016); thus, the strong correlation between $\Sigma[OMPs]_{Cluster\ A}$ and [NO_3^-] implies that the prevalence of OMPs in Kampala surface waters and groundwater was also linked to upstream diffuse pollution such as those originating from urban and agricultural sources. Together, these analyses constitute compelling additional support for the hypothesized importance of wastewater discharges and diffuse runoff as drivers for OMP entry into the aquatic environment of Kampala.

3.4. Potential for biological effects associated with OMPs

Two screening-level risk assessments were performed in parallel to gain exploratory insights into possible ecologically relevant effects of OMPs measured in Kampala samples on aquatic life. To this end, the EAR approach was implemented to screen for the potential for in vitro vertebrate-centric sublethal effects associated with single OMPs or OMP mixtures based on exposure-response metrics derived from molecular bioassay endpoints (Blackwell et al., 2017). Of the 157 OMPs, 136 (including their free and salt forms) had matched entries in the ToxCast high-throughput screening database (U.S. Environmental Protection Agency's Center for Computational Toxicology and Exposure, 2021). Twelve of these OMPs had a median EAR above the precautionary effects-screening threshold of 0.001 (Corsi et al., 2019) under mean exposure conditions. Five cluster B OMPs (i.e., carbamazepine, propylparaben, benzothiazole, fluconazole, and griseofulvin) and 7 cluster C OMPs (i.e., caffeine, 2,4-D, 1,3-diphenylguanidine, diuron, theophylline, DEET, and carbaryl) showed a threshold exceedance in over 50% of the samples. Carbamazepine featured the highest frequency of exceedance (i.e., 100%), followed by caffeine (i.e., 92%), 2,4-D (i.e., 83%), and propylparaben (i.e., 80%), respectively. Consistent with the pattern observed for Σ[OMPs], the median ΣEARs for wastewater and drainage channel water samples (i.e., 43.4 and 21.9, respectively) were two orders of magnitude higher than those for nearshore lake water and groundwater samples (i.e., 0.06 and 0.02, respectively; Figure S7). Two contraceptives (i.e., levonorgestrel and medroxyprogesterone), carbamazepine, caffeine, 2,4-D, and propylparaben constituted the mixture of OMPs that dominated ΣEARs (i.e., 90±11%), but the relative contribution of individual OMPs to ΣEARs varied across sample matrices. For example, levonorgestrel alone contributed to 94±2% of ΣEARs for wastewater samples, whereas levonorgestrel, caffeine, medroxyprogesterone, and carbamazepine collectively explained 88±18% of ΣEARs for drainage channel water samples. Carbamazepine, caffeine, 2,4-D, and propylparaben jointly accounted for 84±14% of ΣEARs for lake water and groundwater samples, with carbamazepine serving as the top contributing compound in the mixture of OMPs.

To complement EAR screening, PAFs and msPAFs were calculated to assess the potential for in vivo lethal effects on aquatic species assemblages associated with single OMPs or OMP mixtures based on log-normal species sensitivity distributions constructed from acute EC50 data (Posthuma et al., 2019). Of the 157 OMPs quantified in Kampala samples, 125 had full species sensitivity distribution data available (Posthuma et al., 2019), but only 1 cluster B OMP (i.e., sulfamethoxazole) and 2 cluster C OMPs (i.e., acetamiprid and imidacloprid) had a median PAF of above 0.1%, indicating low predicted acute toxic pressure posed by individual OMPs. Like ΣEARs, the median msPAFs for wastewater and drainage channel water samples (i.e., 4.6% and 3.8%, respectively) were higher than those for nearshore lake water and groundwater samples (i.e., 0.84% and 0.01%, respectively; Figure S8), although the dominating mixture of OMPs for msPAFs did not overlap with that for ΣEARs. Notably, 40% of wastewater and drainage channel water samples featured high msPAFs (i.e., 5.3–30.6%) that exceeded the generally accepted effect threshold of 5% (Smetanová et al., 2014), suggesting that over 5% of the sensitive aquatic species at sites could potentially be affected by exposure to the mixture of OMPs. Together with norepinephrine and dichlorvos, sulfamethoxazole and two neonicotinoids (i.e., acetamiprid and imidacloprid) explained 84±11% of msPAFs for wastewater and drainage channel water samples. Sulfamethoxazole and the two neonicotinoids also accounted for 99±1% and 88±33% of msPAFs for lake water and groundwater samples, respectively, further underlining their role as potential drivers for the acute toxic pressure posed by the mixture of OMPs.

On average, the fractional contribution of ΣEARs and msPAFs for OMPs never quantified in environmental water samples from Uganda or SSA to those calculated for OMPs quantified in Kampala samples ranged from <1 to 99% and <1 to 88%, respectively. Thus, restricting the calculations of ΣEARs and msPAFs for only OMPs reported in prior work may lead to varying degrees of bias in both indices, particularly when assessing wastewater and drainage channel water samples (**Fig. 5**). Taken together, the EAR and the msPAF calculations provide qualitative evidence for probabilities of sublethal and acutely toxic effects associated with both frequently detected (e.g., carbamazepine, sulfamethoxazole, imidacloprid) and less targeted OMPs (e.g., levonorgestrel, norepinephrine, dichlorvos), which underscores the benefit of applying suspect screening to improve risk-based prioritization of OMPs.

4. Conclusions

Our study combines LC-HRMS based suspect screening with multivariate analysis to comprehensively characterize the occurrence patterns of OMPs and accompanying potential for biological effects in the aquatic environment of Kampala, an urban center in SSA. Our suspect screening approach prioritized and confirmed 157 OMPs, including 24 TPs, in various water samples collected from Kampala. Many of these OMPs have never or rarely been investigated in environmental water samples from SSA. Most OMPs occurred in Kampala samples at concentrations broadly comparable to the ranges reported in prior SSA studies, while others occurred at levels substantially higher or lower than those measured in similar SSA sample matrices, highlighting commonalities and differences in OMP occurrence patterns and the need

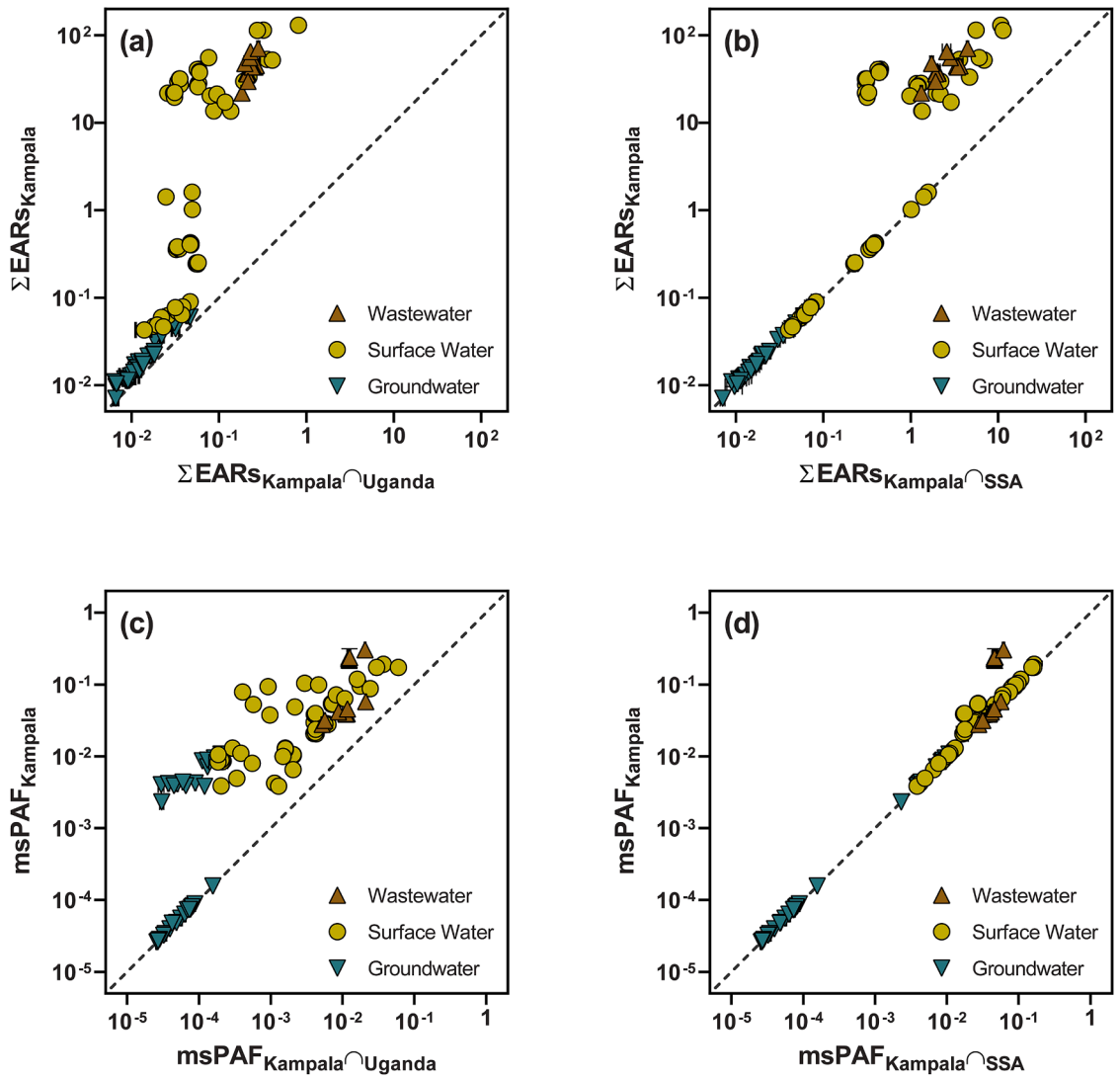


Fig. 5. Comparison of the sample-specific cumulative exposure-activity ratios (ΣEARs) or multi-substance potentially affected fraction (msPAF) for OMPs quantified in Kampala samples versus ΣEARs or msPAF for OMPs measured in both this work and prior Ugandan or SSA studies: (a) Cross plot of ΣEARs for OMPs quantified in Kampala samples ($\Sigma EARs_{Kampala}$) versus ΣEARs for OMPs measured in both this work and prior Ugandan studies ($\Sigma EARs_{Kampala \cap Uganda}$). (b) Cross plot of ΣEARs for OMPs quantified in Kampala samples ($\Sigma EARs_{Kampala}$) versus ΣEARs for OMPs measured in both this work and prior SSA studies ($\Sigma EARs_{Kampala \cap SSA}$). (c) Cross plot of msPAF for OMPs quantified in Kampala samples ($msPAF_{Kampala}$) versus msPAF for OMPs measured in both this work and prior Ugandan studies ($msPAF_{Kampala \cap Uganda}$). (d) Cross plot of msPAF for OMPs quantified in Kampala samples ($msPAF_{Kampala}$) versus msPAF for OMPs measured in both this work and prior SSA studies ($msPAF_{Kampala \cap SSA}$). Error bars indicate the standard deviation of ΣEARs or msPAF; where absent, bars fall within symbols. The dark gray dashed line represents the line of identity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for concerted OMP monitoring in SSA. Moreover, the OMP concentration database compiled for SSA, including data from this work, can facilitate quantitative comparisons of OMP levels in aquatic systems across continents when supplemented with relevant datasets. Our multivariate analysis established the co-occurrence profiles of major OMP clusters and identified the concentration of nitrate and the abundance of a wastewater-derived fluorescent organic matter component as two strong predictors for the sample-specific cumulative concentration of OMPs, which pointed to wastewater discharges and diffuse runoff as potentially important drivers of OMP prevalence in the aquatic environment of Kampala. Measurements of these two water quality parameters can be adapted in resource-limited settings for inference of OMP contamination status but should not be misconstrued as a substitute for OMP analysis. Lastly, our screening-level calculations of EARs and msPAFs supported risk-based prioritization of OMP mixtures exhibiting heightened potential for vertebrate-centric molecular effects and acute toxic pressure; however, no direct extrapolations of these values to ecologically relevant effects on sensitive aquatic species can be made in that the chemical space investigated in this work was limited to polar and semi-polar OMPs amenable to our SPE-LC-HRMS method. Our work is inherently restricted to grab sampling with low spatiotemporal resolution in one SSA urban center due to logistical constraints, but it offers a promising methodological framework for addressing data gaps required for the regional impact assessment of OMPs in other similar settings. We envision growing applications of complementary sampling (e.g., automated or passive sampling), screening (e.g., nontarget screening), and biomonitoring techniques to guide data-driven OMP monitoring and evidence-based ecotoxicological studies in SSA through collaborative research partnerships.

CRediT authorship contribution statement

Shiru Wang: Methodology, Investigation, Formal analysis, Writing – review & editing. **Joseph Wasswa:** Conceptualization, Investigation,

Formal analysis, Writing – review & editing. **Anna C. Feldman:** Investigation, Writing – review & editing. **Isa Kabenge:** Resources, Writing – review & editing. **Nicholas Kiggundu:** Resources, Writing – review & editing. **Teng Zeng:** Conceptualization, Funding acquisition, Visualization, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2022.118706.

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